HPV vaccination: knowledge, attitudes and beliefs in the Chinese population

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Abstract

Introduction

Cervical cancer is the fourth most common cancer in women worldwide. An estimated 62,000 cases of cervical cancer occur annually in China, accounting for 12% of global incidence. Virtually all cervical cancers are related to infection by Human Papilloma Virus (HPV): effective HPV vaccines have been developed and vaccination programmes introduced in many countries over the last decade. Given the burden of cervical cancer in China, it is imperative that effective primary and secondary prevention strategies are introduced. Effective introduction of HPV vaccination programmes will require education and information strategies that are informed by a comprehensive understanding of the knowledge, attitudes and beliefs about HPV infection and its relationship to cervical cancer in the Chinese population.

Aims and objectives

The aims of my thesis are: 1) to systematically review the evidence from the Chinese-language literature in relation to knowledge of and attitude towards HPV infection and HPV vaccination, and 2) to explore knowledge and attitudes about HPV infection, HPV vaccination and cervical screening amongst teenagers in Heilongjiang province in China.

Methods

I undertook a systematic literature review using two electronic Chinese databases – the 'Chinese National Knowledge Infrastructure' (CNKI) database and the 'Wanfang' database. These were searched from inception through November 30th 2012: MeSH terms were applied to both Chinese databases. Manual searching of relevant online journals was also undertaken. Following selection of papers based on pre-determined inclusion and exclusion criteria, quality assessment was carried out using a modified quality assessment checklist, and included studies were classified as good, fair or poor quality. Due to heterogeneity of populations and survey instruments a narrative approach was adopted for data synthesis.

I also undertook a questionnaire survey of high-school students in China. Questions were designed based on the Health Belief Model, informed by findings from my systematic review, and refined through cognitive interviews prior to field work in early 2014. The survey targeted students in five public high schools in one middle-income city (Mudanjiang city) and two small counties (Ning'an and Hailin) of Heilongjiang province; 3788 young

people aged 14-22 years participated. Descriptive statistical analysis was used to summarise demographic characteristics; initially differences were identified using the chi-square test. Factor analysis was applied to identify attitude patterns and logistic regression analysis models were applied to determine the association between attitude (potential predictors) and acceptability, attitude and levels of knowledge.

Results

Forty seven articles met my inclusion criteria and were included in the systematic review. All included studies were published between 2006 and 2011; all were cross-sectional questionnaire surveys with sample sizes ranging from 100 – 9,865. The quality of included studies varied considerably. Included populations ranged from the general public, to young people, and health professionals. Awareness of HPV and knowledge of the relationship between HPV and cervical cancer, and of the sexually transmitted nature of HPV, were the main issues examined. Awareness of HPV was low among all non-health professionals groups. Similarly, understanding of the relationship between HPV infection and cervical cancer and of the sexually transmitted nature of HPV was low. However, significant differences in awareness and knowledge were found, based on urban/rural status, ethnicity and age. Uighur women had the lowest awareness and knowledge levels, followed by rural women adults, and teenagers.

Acceptability of HPV vaccination varied in terms of the vaccine target recipients (whether adult women, or for their daughters), and between health professionals and the general public). Reported levels of HPV vaccine acceptability (for women adults themselves and for their daughters) were higher in North China compared to South China. Health professionals were less willing to accept the vaccine for their daughters than they were to receiving it themselves. The cost, source and appropriate age for HPV vaccination were also frequently examined issues. Importantly, a high proportion of the health professionals believed that the appropriate age for vaccine was over 18 years old for girls.

3788 participants aged 14-22 years were included in the questionnaire survey, with 54% females and 20% urban students. Overall awareness of HPV was 13.2% and acceptability of the HPV vaccine was 68%. Knowledge levels varied in different content areas; for example 74% of respondents knew that HPV vaccination is not 100% effective against cervical cancer while only 6% knew that poor personal hygiene did not increase the risk of contracting HPV infection. Attitudes towards HPV infection and vaccination were also interesting and novel;

the greatest concern about HPV vaccination was minor side effects (72%). The highest-rated source of recommendations about HPV vaccination was parents (66%), while there were concerns expressed about ‘gossip’ in relation to HPV vaccination (51%). No urban/rural differences were found in knowledge and attitudes - gender differences existed, but depended on specific circumstances. Participants who were willing to accept HPV vaccination were more likely to be influenced by others, to report high perceived severity of HPV and cervical cancer, to perceive benefits of HPV vaccination and to score well on knowledge questions. Participants with high knowledge scores for HPV infection and vaccination were more likely to consider HPV infection and cervical cancer to be serious, and were less likely to associate HPV infection with stigma. Participants who had high levels of awareness of HPV infection were more likely to be influenced by others in relation to accepting HPV vaccination.

Discussion

My thesis has produced new and novel findings in relation to HPV vaccination knowledge, attitudes and beliefs in China. Low levels of awareness and knowledge amongst Chinese people may be influenced by traditional Chinese culture, which perhaps makes people more reluctant to consider issues related to sexual practices. Another possible explanation is that people tended to under-report knowledge of HPV when answering the questions in the survey in order to conform to social norms in China - these topics are highly sensitive in China.

High levels of acceptability of HPV vaccines may have also been influenced by ‘ways of thinking’ among Chinese people; their natural inclination is to accept all recommendations for vaccination from government agencies – so they may not have thought hard about this choice. There is optimism in the Chinese population that cancer can be prevented by vaccination – indeed, they are inclined to believe it will prevent disease that can generate serious health impacts in the future. Nevertheless, some Chinese people have conservative attitudes towards the effectiveness of HPV vaccination and some suspicion of the drug companies which produce these vaccines.

There were significant methodological issues in my comparisons of Western and Chinese literature. Western literature is more likely to comprise good quality studies – typically there are better-defined sampling frames, more valid and reliable instruments and robust theoretical frameworks. The difference in quality between Chinese and Western literature arises from the stricter rules for reporting and evaluation in western publications and the relatively low publishing standards in Chinese literature.

My thesis also details a number of methodological issues which arose in conducting my questionnaire survey – ideally, I would like to follow up the work I have done with a multi-centre population-based study among teenagers in China (an idea which I will pursue once I return to China). This would hopefully provide better quality information on the influences of factors such as socio-economic status and family background in determining acceptability of HPV vaccination. Nevertheless, my relatively modest, school-based study has, I believe, produced results which add to the information available to health care planners and policy makers in the field of HPV vaccination in China.

Conclusion

My systematic review is, to my knowledge, the first to identify and synthesise findings about knowledge of and attitude towards HPV infection and vaccination in the Chinese literature – as such, it addresses a gap in currently available evidence. Although there are methodological limitations in Chinese literature (with more poor quality studies), the results still have implications for further health education intervention programmes and health policy.

My questionnaire survey was also a 'first' in many ways – it explored attitudes towards HPV vaccines based on Health Belief Model among Chinese teenagers and examined HPV related stigma among mainland Chinese teenagers. Low levels of awareness and knowledge and conservative attitudes towards sexually related infections suggest the impact of Chinese traditional culture and a range of other social and financial constraints in China. Hence, there is a great deal to be done before HPV vaccination can be implemented in China – there are educational needs, and in many areas societal and cultural attitudes need to be challenged. Significant changes are also need in government policy and investment – these are major challenges for health care in China, and I sincerely hope my thesis will contribute to these important debates.

Declaration

In accordance with University regulations, I declare that this thesis has been completed by me and that the work presented is my own, except where acknowledgement has been made in the text. No part of this work has been submitted for any other degree or qualification.

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Du Wang

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Finally, I am grateful to my parents Weimin Wang and Yanfang Li, and my husband Xiaofeng Liu for their financial and psychological support, encouragement and patience throughout my PhD.

List of abbreviations

ACC	Adenocarcinoma
ASC-H	Atypical squamous cells
ASC-US	Atypical squamous cells of undetermined significance
ASR	Age-standardised rate
CDC	Centre for Disease Control
CI	Confidence interval
CICAMS	The Cancer Institute/Hospital of the Chinese Academy of Medical Sciences
CIN	Cervical intraepithelial neoplasia
CIS	Carcinoma in situ
CNKI	China National Knowledge Infrastructure
DALYs	Disability-adjusted life years
DNA	Deoxyribonucleic acid
EDA	Exploratory data analysis
EPI	Expanded Programme on Immunisation
FDA	US Food and Drug Administration
FSW	Female sex workers
GAVI	A global Vaccine Alliance
GDP	Gross Domestic Product
GSK	GlaxoSmithKline Biologicals
HBM	Health Believe Model
HBV	Hepatitis B virus
HC2	Hybrid Capture Assay 2
HIV/AIDS	Human immunodeficiency virus /the acquired immunodeficiency syndrome
HPs	Health professionals
HPV	Human papillomavirus
HR	Hazard ratio
HR-HPV	High-risk HPV
HSIL	High-grade squamous intraepithelial lesions
IARC	International Agency for Research on Cancer
ICC	Invasive cervical cancer
ICESCC	International Collaboration of Epidemiological Studies of Cervical Cancer
INNOVAC	The name of an Chinese pharmaceutical company producing HPV vaccine
LR-HPV	Low-risk HPV
LSIL	Low-grade squamous intraepithelial lesions
MC	Male circumcision
MDGs	Millennium Development Goals
MSM	Men who have sex with men
NCDs	Non-communicable disease
NHFPC	The National Health and Family Planning Commission in China
NIP	National Immunisation Plan
OCP	Oral contraceptive pill

OR	Odds ratio
PCR	Polymerase chain reaction
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALYs	Quality-adjusted life years
RCT	Randomised control trial
SCC	Squamous cell carcinoma
SCT	Social Cognitive Theory
SIL	Squamous intraepithelial lesions
STI	Sexually transmitted infection
TPB	Theory of Planned Behaviour
TRA	Theory of Reasoned Action
TTM	Transtheoretical Model
UNICEF	United Nations Children's Fund
VIA	Visual inspection with acetic acid
VLPs	Virus-like particles
WHO	World Health Organisation

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1 Chapter 1 Introduction/Background

1.1 Cervical cancer

My thesis examines HPV vaccination, cervical cancer and cervical screening in China. I begin with an overview of cervical cancer in China and internationally. Cervical cancer is the fourth most common cancer among women worldwide [1] and is usually classified into two main types: squamous cell carcinoma (SCC),which contributes to 75% of all cervical cancer cases, and adenocarcinoma (ACC) [2].

Before invasive cervical cancer (ICC) (commonly called cervical cancer) develops, precancerous lesions occur including different grades of dysplasia, ranging from mild to severe [2, 3]. Dysplasia, diagnosed based on histology, is a term describing the cell changes in epithelium[4]. Grades of dysplasia are defined in terms of the location of cell changes in the various layers of epithelium[4]. The nearer the dysplasia occurs to the basal layers, the higher the risk of the development of cervical cancer. If the lesions are found in the basal membrane, invasive cancer is diagnosed [2-4].

There are two precursor phases of cervical cancer: cervical intraepithelial neoplasia (CIN; diagnosed histologically by biopsy) and squamous intraepithelial lesions (SIL; defined by cytology screening) [2]. CIN1 (cervical intraepithelial neoplasia grade 1) and LSIL (low-grade squamous intraepithelial lesions) normally occur in the superficial layers of epithelium; CIN2 and HSIL (high-grade squamous intraepithelial lesions) in the intermediate layers; and CIN3 and HSIL in the basal layers[4, 5]. Figure 1-1 shows different grades of CIN occurring in various layers of epithelium.

1.1.1 Classification of cervical cancer

Four systems of classification of cervical cancer are used worldwide [3]. Two systems (the Papanicolaou system and the Bethesda system) based on cytology are used for cervical screening; two others (the Richart system and the Reagen/WHO system) based on histology are used for diagnosis of cervical lesions and cancer[3]. Table 1-1 shows the classification systems for cervical screening and diagnosis [3]. Precancerous lesions are often asymptomatic and are usually discovered by cytological examination (Pap smear screening) [5].

Table 1-1: Classification systems for cervical screening and diagnosis

<table>
<tr><td colspan="2">Cytological classification (for screening)</td><td colspan="2">Histological classification (for diagnosis)</td></tr>
<tr><td>Papanicolaou system</td><td>Bethesda system*</td><td>Richart system*</td><td>Reagen/WHO system</td></tr>
<tr><td>I</td><td>Normal</td><td>Normal</td><td>Normal</td></tr>
<tr><td>II</td><td>ASC-US, ASC-H</td><td>Atypia</td><td>Atypia</td></tr>
<tr><td rowspan="4">III</td><td rowspan="2">LSIL</td><td>Condyloma</td><td rowspan="2">Mild dysplasia</td></tr>
<tr><td>CIN1</td></tr>
<tr><td rowspan="3">HSIL</td><td>CIN2</td><td>Moderate dysplasia</td></tr>
<tr><td rowspan="2">CIN3</td><td>Severe dysplasia</td></tr>
<tr><td>IV</td><td>Carcinoma in situ (CIS)</td></tr>
<tr><td>V</td><td>Invasive carcinoma</td><td>Invasive carcinoma</td><td>Invasive carcinoma</td></tr>
</table>

ASC-US: atypical squamous cells of undetermined significance; ASC-H: atypical squamous cells where it is not possible to exclude a high-grade squamous epithelial lesion.
* Both the Bethesda system and the Richart system are used in China for cervical screening and cervical cancer diagnosis.
Reproduced from *World Health Organization Guide: Comprehensive cervical cancer control* [5] with a slight adaptation.

1.1.2 Natural history of cervical cancer

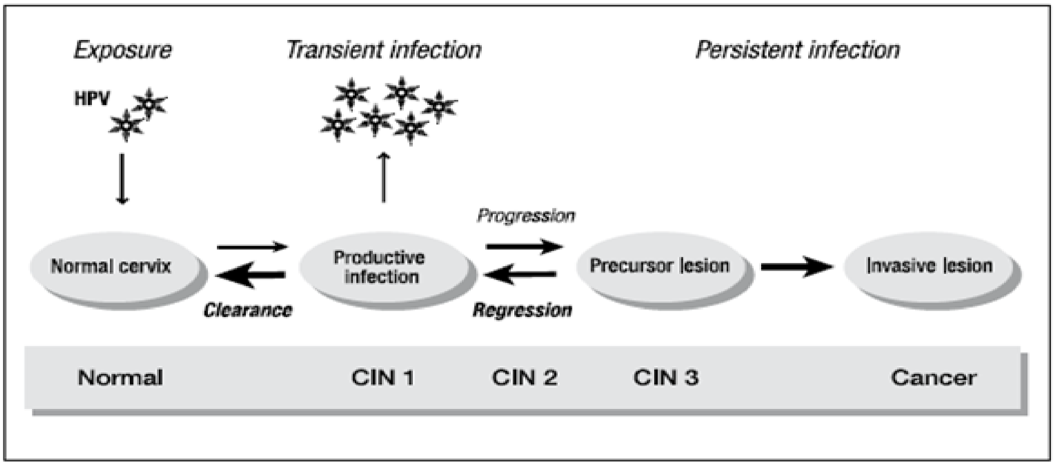
Precancerous lesions normally exist for an extended period of time, during which regression and progression can occur, depending on the various grades of lesions [2, 3] (see Figure 1-1 and Table 1-2).

Table 1-2: Natural history of cervical cancer

Classification of precursor lesions	Natural history		
	Regress	Progress to CIN3	Progress to ICC
CIN1	57–90%	11%	1%
CIN2	43–55%	22%	5%
CIN3/CIS	32%		>12%

Reproduced from *Cervical Cancer Studies on Prevention and Treatment* [6]with a slight adaptation

Figure 1-1: Natural history of cervical cancer



CIN: cervical intraepithelial lesion

Reproduced from *World Health Organization Guide: Comprehensive cervical cancer control* [5] which is adapted from *Cervix Cancer Screening, Lyon, IARC Press, 2005*. [7]

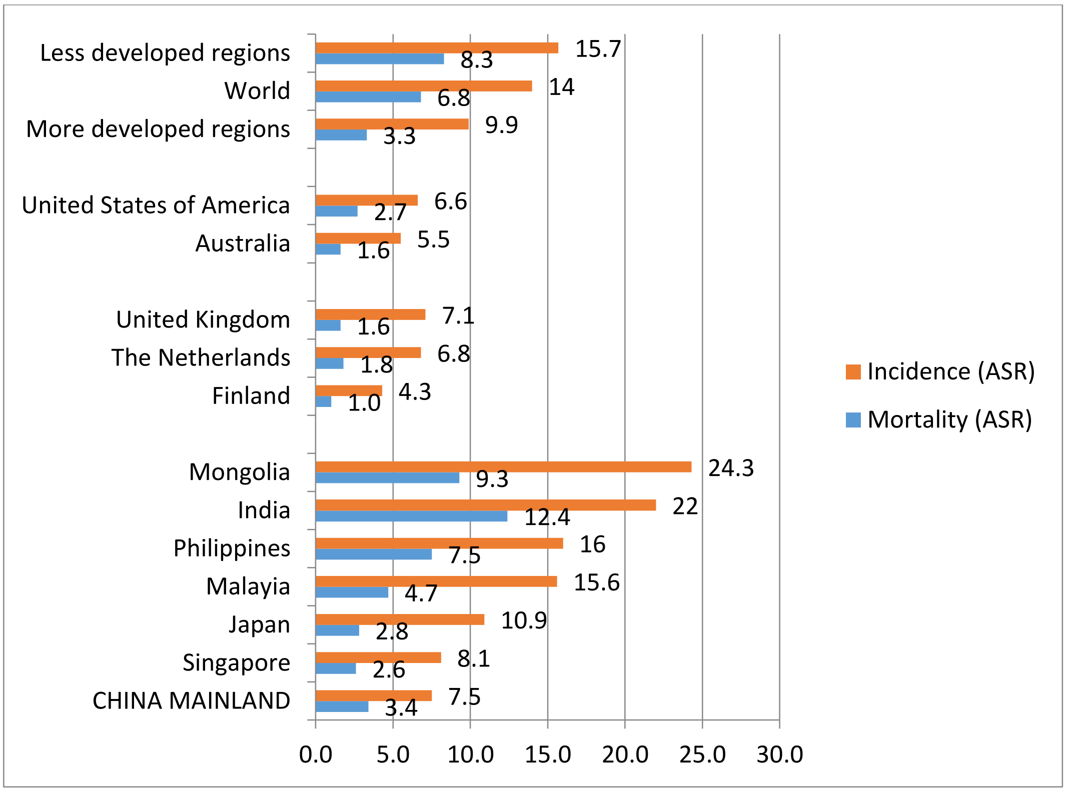
Regression: Most precancerous lesions regress spontaneously without treatment [5, 8]. The respective likelihood of regression and progression depends on the CIN grade [6, 8]. Up to 80% of CIN1 lesions will regress, reaching up to 90% in adolescents and young women under 25 years old [6, 8]. Up to 55% of CIN2 will regress within 4–6 years [6, 8]. CIN3 will regress in one third of the cases [6, 8].

Progression: If precancerous lesions are not treated appropriately, they may progress and eventually lead to invasive disease. But prior to the occurrence of invasive cancer, precancerous lesions are entirely reversible[5]. The link between HPV infection and cervical cancer is now well established; there are four stages in the progression from Human Papillomavirus (HPV) infection to cervical cancer, they are: HPV transmission, acute HPV infection, persistent HPV infection leading to precancerous lesions, and ICC (invasive cervical cancer) [5]. The risk and the time taken for progression to cervical cancer largely depend on the persistence of specific HR-HPV (high-risk HPV) types and the grade of CIN [8]. The average total time from HR-HPV infection to the development of ICC is 25–30 years. CIN3 have a 90% likelihood of progressing to ICC, and it is estimated that more than 12% of CIN3 cases progress to ICC if not properly treated[9]. However, the rate of progression to ICC is low for CIN1 (1%) and CIN2 (5%)[4, 6]. Positive cases of HPV 16 and 18 with low-grade lesions are more likely to progress to high-grade disease and ICC than other HPV types [8].

1.1.3 Cervical cancer epidemiology

An estimated 62,000 new cases of cervical cancer occur annually in China, accounting for 12% of the total new cases worldwide, which stands at approximately 528,000 women in 2012[1, 10]. Around 30,000 deaths from the disease occur annually in China, out of 266,000 deaths worldwide in 2012 [1]. As predicted by the World Health Organisation [2], if the incidence rates do not drop and instead remain constant over time in China, the annual number of new cases of cervical cancer will increase by 85% in the over-65 age group by 2025; a similar projection is given in relation to the annual number of deaths by 2025. However, the projected burden is smaller in developed countries such as the UK. By 2025, the annual number of new cases and deaths is predicted to increase by 27% in the over-65 age group in the UK [2]. Figure 1-2 presents the age-standardised incidence and mortality rates in selected countries across different continents, based on the WHO report of 2014 [1].

Figure 1-2: Age-standardised incidence and mortality rates for cervical cancer in selected countries in 2014



Adapted from WHO report: *Human Papillomavirus and Related Diseases 2014 [1]*

Incidence

WHO and IARC Report

The WHO reported in 2010 that the age-standardised rate (ASR) of incidence of cervical cancer was 7.5 per 100,000 women in China, compared with 14.0 per 100,000 women worldwide [1]. However, no national cancer registry exists in China, and the incidence rate of cervical cancer is estimated by modelling from sample surveys, which may not be representative of China overall. In the WHO report, of 36 Chinese cancer registries, fifteen registries (Hong Kong, Macao and Taiwan are excluded because of potential bias) were able to monitor cervical cancer incidence rate between 1993 and 2007 with any degree of reliability [1]. The age-standardised incidence rate ranged from 0 per 100,000 women in Changle to 71.8 per 100,000 women in Yangcheng [1]. The data were also reported in *Cancer incidence in five continents IX* by the International Agency for Research on Cancer (IARC) [10-12]. However, seven of the fifteen registries are Tier one cities (capital city in the province or municipalities such as Beijing and Shanghai) where the annual income of residents is 1.3–3 times higher than the national average (the Gross Domestic Product (GDP) per capita is also higher than average) [1, 10, 11]. The remainder were less-developed counties. Incidence of cervical cancer by histology in China have been reported in only five cancer registry between 1998-2002, four of which are Tier one city [1]. Thus, direct comparisons of the incidence rate between cancer registries and other unavailable regions should be made with caution due to limitations on the accuracy and availability of data.

National Centre for Cancer Registries Report

The incidence rate reported by the National Centre for Cancer Registries of China was obtained from 1998 to 2006 based on more than 30 sites (the number of sites varied each year). But the proportion of the total population covered was consistently small, standing at less than 6% of the national population. In the last three reports (2004, 2005 and 2006), the overall cervical cancer incidence rate was 6.0–9.1/100,000 women reported, and no substantial difference between urban and rural areas was identified [10, 13-15] .

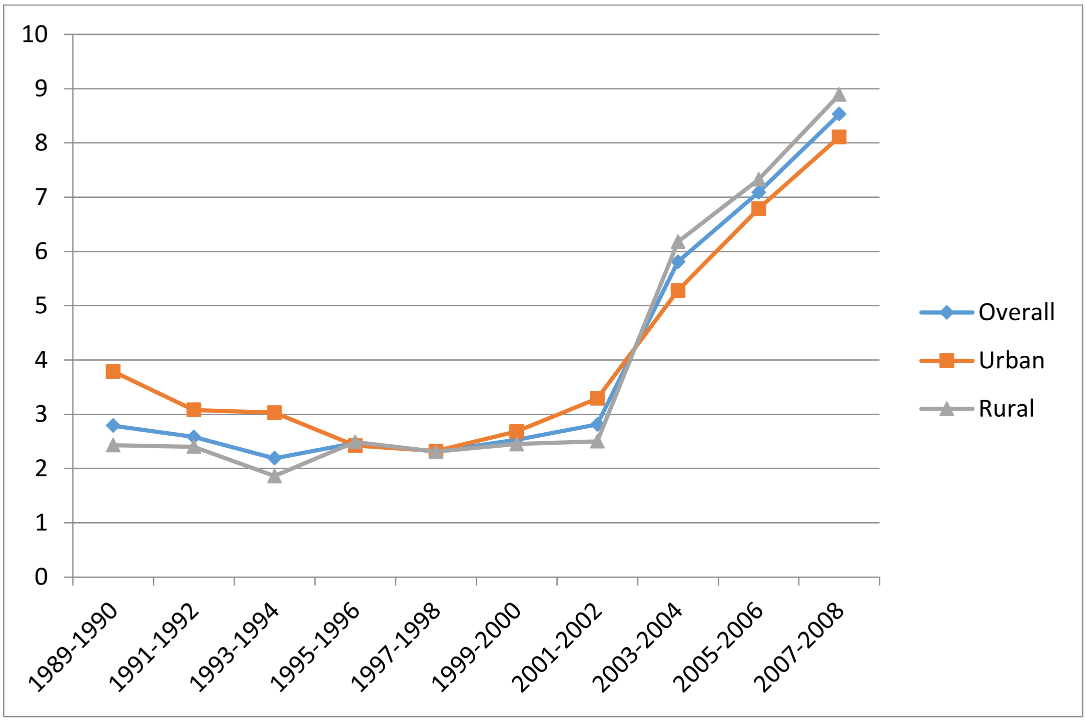
Cancer Registries Latest Report

The most recent report on the cervical cancer incidence rate was published in 2014 in Chinese[16]. It analysed the trend of cervical cancer incidence and mortality rates among Chinese women during 1989–2008, and is considered to be the most comprehensive and objective study assessing the burden of cervical cancer in China in the recent decades. The overall ASR incidence reported between 2007 and 2008 was 8.53/100,000 women, 8.11/100,000 in urban areas and 8.89/100000 women in rural areas [16-18].

The data came from 41 cancer registries, which were established in China to record the cancer incidence rate and mortality rate up to 31 December 2008[16]. They covered 31 provinces/autonomous regions/municipalities, including 32,798,187 Chinese women, accounting for only 5% of national population in the whole country[16]. Population data were obtained from the local police department, where information about citizens' identity was stored[16]. Further, 9 of 41 cancer registries have continuous data through 1989–2008, covering approximately 22 million people. The sub-analysis of the trends of the cervical cancer burden based on the nine cancer registries was equivalent to the trends from the 41 cancer registries [16-18].

Differences exist between the people covered by these registries and the national Chinese population in terms of the proportion of urban and rural residents[16]. Thus, adjustments were made when the incidence and mortality rates were estimated. But economic status (ie annual income), social status, ethnicity, and education levels were not adjusted, suggesting that the composition of the population covered by the cancer registries could not be considered representative of the national population as a whole. Although bias may exist, the estimate of cervical cancer burden provided by this study is thought to be the most reliable in China due to the data integration of national cancer registries and the adjustment made to the proportion of urban/rural residents[16]. The 41 cancer registries were the selected qualified registries based on the requirement of registration quality in *Cancer incidence in five continents IX* [12, 16]. Figure 1-3 presents the trends in ASR of cervical cancer during 1989–2008 [16-18].

Figure 1-3: Trends in age-standardised incidence rate for cervical cancer by urban/rural regions in China



Reproduced from Tables 1 and 2 of *Trend Analysis of Cervical Cancer Incidence and Mortality Rates in Chinese Women During 1989–2008.* [16]

Trends of ASR in cervical cancer

The incidence dropped before 1997, but a significant increase was observed from 1999 to 2008, with an annual increase rate of 8.7% (crude incidence rate) nationally; the increased rate was higher in rural regions than urban regions [16-18]. In the contrast, most countries and regions experienced a downward trend of cervical cancer incidence over the past decade.

Developed countries have seen an annual decrease rate of 2–4% over the past two decades, largely attributable to screening activities[19]. For example, the US [19] had an annual decrease rate of 1.8–3.6% (Black and White) during the period of 1975–2009; the UK [19] reported that incidences of cervical cancer declined by 4.1% annually from 1983–2007.

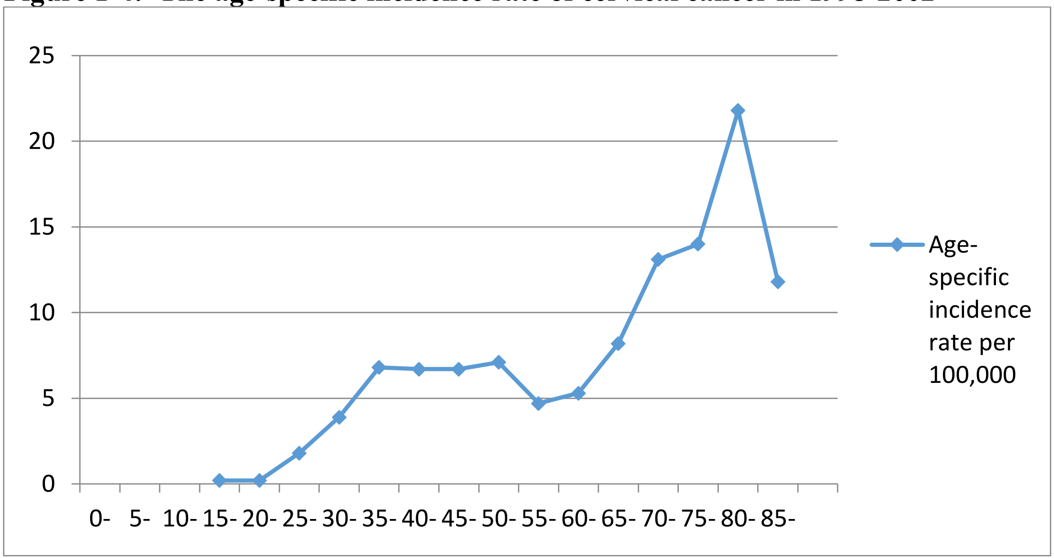
A downward trend was generally observed in most developing countries during the period of 1980–2002, with the exception of Thailand and Uganda; the average annual drop in incidence was 1.5–4.1%[19]. However, the data comprised only partial information from limited cancer registries, and was thus not representative of large and heterogeneous countries such as India and China. During the last decade, data have been unavailable or have not been summarised in countries such as Brazil, Philippines, Thailand, India, and China [19]. Thus, comparisons cannot be made between developing and developed countries. There are difficulties in identifying a typical pattern of cervical cancer incidence in developing countries over the last decade.

The potential factors contributing to the trend in the cervical cancer burden in China during the period 1989–2008 are as follows. First, the diagnostic criteria for the pathology of cervical cancer did not change over the period, and before 2009 no large national cervical screening programmes were undertaken. Hence, theoretically, the detection rate would not have changed significantly. Second, the downward trend before 1997 may be attributable to the improvement in overall health conditions, along with a growing economy in the whole country after the *Reform and Opening Up* policy (major social reform initiative in China, which started in 1978). Third, the remarkable upward trend after 2000 may be partly a reporting effect, but also potentially due to the cumulative result of exposure to risk factors. These include changes in sexual attitudes and behaviours (becoming sexually active at a younger age, multiple sexual partners, and unprotected sexual activity, etc.), brought about by the social change that followed the Opening Up. Also, the establishment of a primary care system is still lacking progress (inadequate primary and secondary prevention, including health awareness, education, and screening, etc.). The *Reform and Opening Up* policy brought better health care, but, on the other hand, lifestyle changes led to higher-risk behaviours, which were riskier still because of the inadequacy of primary care.

The pattern among different age groups

Age-specific incidence rates comprised fewer than 10 cases per 100,000 women aged under 44, which is similar to global rates. One peak was observed in most developed countries at about 50–60 years after the rise from the age of 30–35 [3]. Two such peaks were observed in rates in China[18]. The first one was observed between the age of 40–44 years (18.7/ 100,000), and the second was at 80–84 year old (13.9/100,000); the rates then dropped immediately after the peak. The data were obtained from 1990 to 1992 and reported by the National Office for Cancer Prevention and Control in 2008 [18]. Another two-peak pattern was reported in 2008, with data from 1998 to 2002. The first peak was seen at age 35–54 years (6.7–7.3/100,000) and the second one was in women aged over 65 years (8.8–21.3/100,000) [18]. Geographically limited data sources and a variety in cancer reporting and registration systems may explain the different patterns. Most developing countries have the pattern of the two peaks of ASR of incidence, with one peak at approximately 45 years old and another peak at 55 years old, but not equivalent to those of China [2]. Figure 1-4 presents the age-specific incidence rate of cervical cancer with two peaks, based on 5 cancer registries from 1998 to 2002 [17].

Figure 1-4: The age-specific incidence rate of cervical cancer in 1998-2002



Reproduced from *Epidemiology and Prevention of Human Papillomavirus and Cervical Cancer in China and Mongolia* [17]
The data was obtained from on 5 cancer registries.

It is difficult to explain why two peaks in the rates occurred in China. The data came from 5 cancer registries a decade ago in China, whereas there are now 41 cancer registries covering

31 provincial regions. Thus, the two-peak pattern generated is probably not reliable or representative.

Geographical differences

Incidence rates are also affected by geographic area – although again there are limitations on the accuracy of the data. Yangcheng of Shanxi Province in China has a very high incidence rate—81 cases per 100,000 women in 2008 [17]. Kashi Prefecture in Xinjiang Uyghur Autonomous Region had an increase in the prevalence of cervical cancer from 459 cases/100,000 women in 1991 to 622 cases/100,000 women in 2007. Between 2010 and 2011, the prevalence of cervical cancer was 407 cases/100,000 among low-income Muslim Uyghur women aged 30–59 years [20]. As an incidence rate of cervical cancer in Xinjiang region cannot now be obtained, it is more difficult to make comparisons between Xinjiang region and other regions in China and to estimate the level at which Xinjiang stands.

Mortality

WHO and IARC Report

The WHO reported in 2010 that the age-standardised mortality rate for cervical cancer was 4.5 per 100,000 women in China and 7.8 globally. It interpreted data on China obtained from the Third National Death Survey from 2004 to 2005 for rural and urban populations in three regions (East, Middle, and West) [2]. The Third survey used multistage stratified cluster sampling with proportional allocation, covering 11% of total population in 31 provinces, autonomous regions, and municipalities [10, 16]. The mortality rate in the 2014 WHO report was lower (3.4) - an estimation for 2012 by modelling using data in 23 cancer registries (covering 6% of the population) between 2004 and 2010 [1].

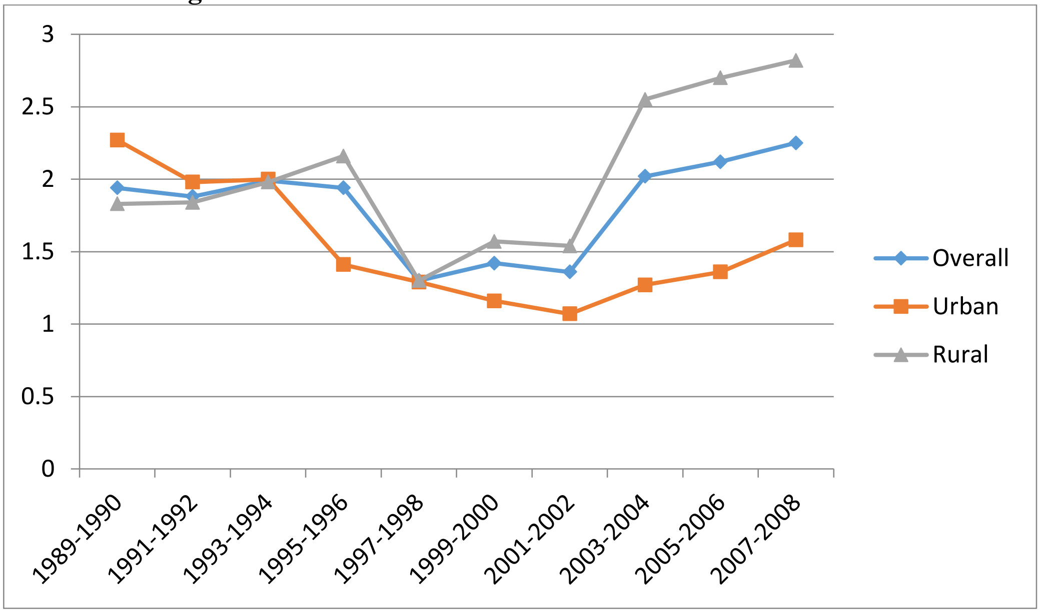
Cancer Registries Latest Report

The recently published Chinese-language study (2014) summarised the crude and age-standardised mortality rate of cervical cancer in the period 1989–2008[16]. The study was based on 41 cancer registries in China, covering 5% of the total Chinese population. The urban ASR mortality rate was 1.58 per 100,000 women, and the rural ASR mortality rate was 2.82 per 100,000 women in 2008; the overall ASR was 2.25/100,000 women [16].

ASR trends in cervical cancer

The cervical cancer mortality rate initially experienced a downward trend, followed by an upward trend during the period 1989–2008. Evidence suggested [10] the downward trend of mortality occurred between 1987–1989 and 1997–1999. In rural areas the decrease in mortality was found to be 34% in women aged over 50 years, although the average rate remained constant over the period. In urban areas, the mortality reduction in women aged over 50 years was greater, at 61%, but remained low and stable for women younger than 50 [10]. After 2000, an upward trend in mortality rates was found, which was an 8.1% annual increase in crude mortality rates (7.3% annual increase in urban areas after 2001, and the rural annual increase was not significant after 2001) [16]. Figure 1-5 presents the trends in mortality ASR of cervical cancer.

Figure 1-5: Trends in age-standardised mortality rate of cervical cancer by urban/rural regions in China



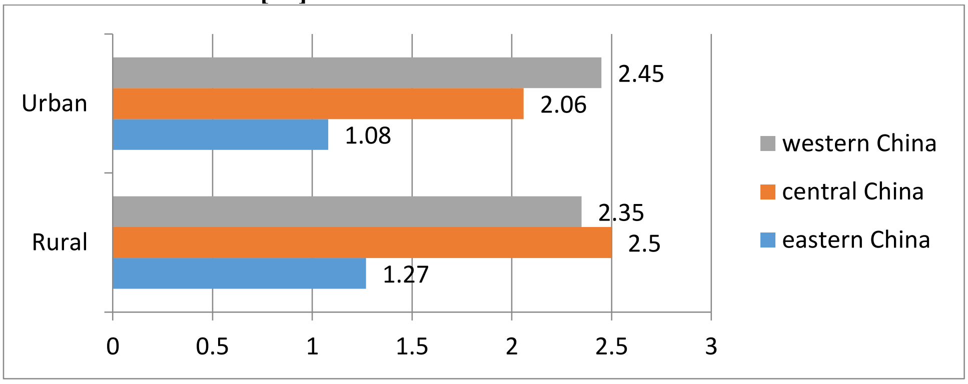
Reproduced from Tables 1 and 2 of *Trend Analysis of Cervical Cancer Incidence and Mortality Rates in Chinese Women During 1989–2008.* [16]

The factors contributing to the mortality pattern are generally the same as those for the incidence pattern. The *Reform and Opening Up* policy starting from 1978 was the major influencing factor. It is thought to have been associated with the reduction of incidence and mortality in the earlier years, but potentially increased the likelihood of exposure to risk factors without an ability to access prevention programmes in time.

Geographical difference

Mortality rates vary by geographic area [11]. Western and central China had the highest mortality rates for cervical cancer (36/100,000 women in Wudu County, Gansu Province and Yangcheng County, Shanxi Province), while eastern China had the lowest [17]. The geographic comparisons are shown in Figure 1-6. Generally, western and central China are deprived regions compared to eastern China, and regional inequalities in health exist in China [21, 22]. Western regions (e.g. Xinjiang, Qinghai) in China are lacking of adequate health recourses and health services, which may make residents less likely to have constant access to health care than residents in eastern more developed regions. Further, deprived people (in rural regions) tend to have intercourse for the first time and give birth at a younger age - generally three and four years earlier than people in urban regions [11]. These factors may explain the regional differences in incidence and mortality rate.

Figure 1-6: Age-standardised mortality rate for cervical cancer in different regions of China in 2004–2005 [18]



Ethnic difference

There are also variations in cervical cancer mortality between different ethnic groups. The three ethnic groups with the highest mortality rates are the Uygur ethnic group in Xinjiang (17.2 per 100,000), the Mongolian ethnic group (15.7), and the Hui ethnic group (12.2) [18]. These three groups mostly reside in specific autonomous regions. They are very closely related to geographical areas and socio-economic conditions. For example, Xinjiang autonomous region, located in the West China, is a deprived area with less developed health care and education systems.

Five-year survival

Some data suggest the five-year relative survival rate for cervical cancer in the period 2000–2002 in China was higher (67%) than in most developed countries, such as the UK (58.6–63.5%) and the US (65.8%) [23]. But the 95% confidence interval is too wide to be reliable, the reliable range being 48–79%. Access to the latest data in China (covering the last decade) is not yet available. The lack of registries and incomplete health informatics systems may explain the unreliable and unavailable data. The five-year survival rate also depends on the stage of cervical cancer. The earlier the stage of cervical cancer, the higher the five-year survival rate. A worldwide multicentre study [24] (37 countries) of 11,775 patients treated between 1999 and 2001 reported that Stage I (the carcinoma is strictly confined to the cervix) cervical cancer patients had an over 75% overall survival rate at five years, and rate was over 65% for Stage II (the cervical carcinoma has invaded beyond the uterus, but not to the pelvic wall).

1.1.4 Summary

The incidence pattern typically seen in many countries around the world (one peak of incidence ASR) is not so recognisable in China. Although the two-peak pattern was observed in many developing countries (in Asia and Africa), the pattern in China is not typical of a developing country, as it was different from other countries (India and Africa) in terms of the age range of each peak [2]. Developed countries in America, Europa, and Oceania have generally the same incidence pattern, with only one peak at approximately 45 years old [2].

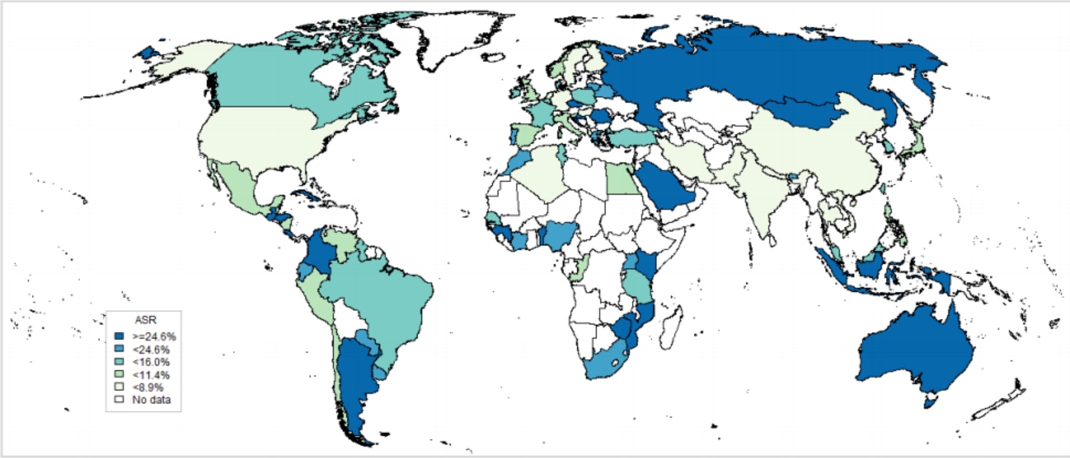
The mortality trend (first downward, then upward from the year 2000) in China appears to relate to the economic impact and social transition of the recent decades.

The transition of demography and economy in the last two decades in China may explain the different pattern of incidence and mortality of cervical cancer from that of other countries. The *Reform and Opening Up* policy (market economy reform) lead to the growth of the economy, the improvement of health conditions, and the migration of people for better jobs in big cities. It also contributes to the changes in sexual attitudes: having sexual intercourse at an earlier age, multiple sexual partners, and less monogamous relationships long-term separation from families (because of the migration for work).

1.2 Human Papillomavirus (HPV)

Given the focus in my PhD on HPV vaccination, I report some background information on HPV. HPV infection is one of the most common sexually transmitted diseases. Worldwide, the estimated age-adjusted global prevalence of HPV is 11.7% [25]. Prevalence will be up to 30% in women under 25 years old [4]. The overall HPV prevalence among women is higher in developing regions (14.3%) than developed regions (10.3%). But, since data concerning HPV prevalence cannot be obtained for most developing countries - especially in Africa, Central Asia and East Europe (See Figure 1-7), it is difficult to examine differences between low-resource and high-resource countries[2]. China has an overall HPV prevalence of 12.2%, but this is likely to be an underestimate because of the lack of available and reliable data sources in China (the available data were obtained from research-based studies in various parts of China, mostly in the developed regions)[2].

Figure 1-7: World prevalence of HPV among women with normal cytology



Reproduced from WHO 2014 on *Human Papillomavirus and Related Diseases* [1]

A trend was reported in the female age-specific distribution of HPV. HPV prevalence peaks among young women under 25 years old in most geographical regions worldwide [2]. Further, a second peak of prevalence, in women aged 45 years or older, is found in Central America, South America, and Africa. In contrast, HPV prevalence in males generally remains stable or declines slightly after the peak [26].

Chinese studies [11] also reported two peaks of HPV prevalence among Chinese women (discussed later in this chapter). But the pattern is unlike the one in developed countries, where a general downward trend was observed. The social transition in China over the past decades along with the *Reform and Opening Up* policy may explain the difference from other countries in the world.

The age-specific overall HPV prevalence in China follows an expected pattern, especially when taking into account the pattern of ASR incidence of cervical cancer. Similarly, two peaks were observed and the peak of HPV prevalence occurs slightly earlier than ASR incidence of cervical cancer. The first peak is among 15–24-year-old women, with a 16.2% prevalence, and the second peak is at 35–39 years, with a prevalence of 18.6% [11]. The differences from developed countries are explained by the new acquisition or reactivation of latent HPV infections [27].

1.2.1 The natural history of HPV infection

Most HPV infections are transient and asymptomatic. Between 60 and 80% of new HPV infections clear within 12 months, and 90% within 24 months [4]. Only 10–30% of infections will persist over 1 or 2 years and thus have the potential to lead to the transformation of epithelium in cervix. Studies have shown that the average duration of infection is usually 4–20 months (the median duration is 8 months), and HR-HPV types will persist longer than LR-HPV types[28]. Between 1 and 10% of persistent HPV infection cases may develop dysplasia in 0.5–5 years and finally progress to cancer through several stages[4].

1.2.2 Virology and immunology of HPV

Structure of the HPV virus

The HPV virus is a non-enveloped, double-stranded segment of DNA in the Papovaviridae family, with the DNA wrapped by two capsid proteins: the major protein is L1, and the minor one is L2. Apart from structural genes (L1 and L2), several early genes (E1, E2, E4, E5, E6 and E7) help to interact with the host genome [6]. These genes and proteins are used for virus transcription and replication, are expressed in various layers of epithelium, stimulate the proliferation of infected basal cells, and are internalised by host cells, finally leading to invasive disease [6].

Clearance of HPV virus

Most HPV infections are transient and are automatically cleared by the host immune response without causing lesions [29]. But the mechanism behind this is still not well understood. Two possible explanations are: complete viral clearance and extremely low levels of virus replication with incomplete viral expression. HPV infections that are not cleared can persist for a long period in the infected epithelium, which can progress to low-grade lesions (LSIL, CIN1) or directly to high-grade lesions (HSIL, CIN2, CIN3) and in turn progress to invasive cancer [29].

Immunology and integration with host cells

Two pathways can be identified which are involved in the immunology of HPV infections of host cells [29]. First is a humoral immune response, taking approximately 6–18 months and producing neutralising antibodies against a type-specific L1 epitope. The antibodies are useful to prevent an initial HPV infection but not sufficient to fight against new infections [29]. Second, the HPV makes contact with the basal membrane and starts integration with the epithelial cell and basal membrane by L1 of the HPV virus. However, the integration process is still unclear [29]. After integration, L1 and L2 are shed from the epithelial cell and the L1 antibody does not work. Then cytotoxic T cells start to react, recognising the expressed viral proteins (E6 and E7) and in turn fight against HPV epitopes. The effectiveness of the host's immune response affects how well the HPV infection is cleared. People with HIV are at higher risk of getting persistent HPV infections [29].

Influencing factors of HPV virus persistence

Several factors affect the persistence of the HPV virus in the human body. They are: specific types of virus (HR-HPV, LR-HPV), co-infection with multiple HPV types, and HPV viral load [30]. First, HR-HPV, such as HPV 16 and 18, present a higher risk of progressing to high-grade lesions. Epidemiological studies have shown HPV 16-positive women had a 17% cumulative incidence rate of developing high-grade lesions; the rate is 13% for HPV 18-positive women. In contrast, the 10-year risk for LR-HPV-positive women is 3% [30]. Second, co-infection with multiple HPV types is another factor in HPV viral persistence, but the mechanism for this is not clear. It is difficult to determine whether it is the modification of the persistence of a given HPV type or of the progression to high-grade lesions/invasive cancer that contributes to the persistence of the HPV virus by co-infection with multiple HPV types[30]. Third, the HPV viral loads, defined by the number and size of HPV, are considered to be one of the factors of HPV viral persistence. Studies have shown low viral loads have a low risk of developing precancerous lesions/invasive cancer. However, high viral loads have not been clearly confirmed to be associated with a high risk of development of cervical cancer, as some of the highest viral loads have been found to contribute to the regression of low-grade lesions [30].

1.2.3 HPV and cancer (especially cervical cancer)

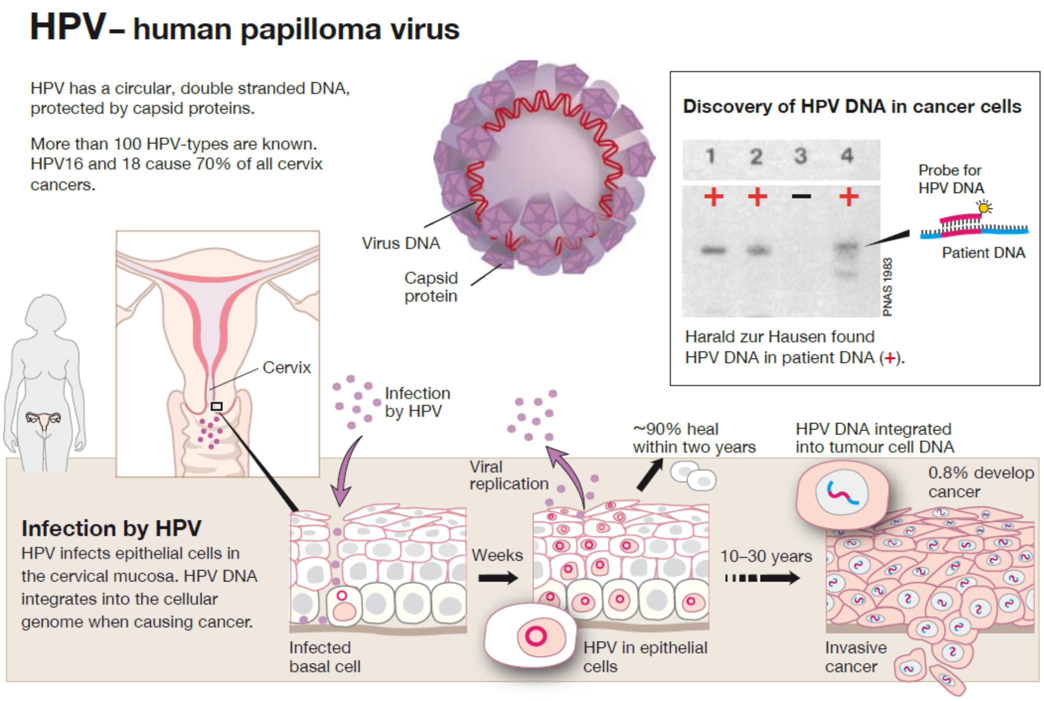
The 2008 Nobel Prize [31] was awarded to Harald zur Hausen for his discovery of "human papilloma viruses causing cervical cancer". He assumed in the 1970s that HPV caused cervical cancer, found novel HPV-DNA in cervical cancer biopsies, and thus discovered HPV 16 type in 1983 and cloned HPV 16 and 18 from cervical cancer patients in 1984 [31]. Figure 1-8 presents the structure of the HPV virus and how it integrates into tumour cell DNA in the cervix.

It has been 40 years since the initial hypothesis that HPV causes cervical cancer. Many biological and epidemiological studies have confirmed the association between HR HPV and cervical cancer.

Biological evidence

There are no confirmed biological mechanisms that completely explain how HR HPV causes cervical cancer, but the most accepted one is that the first step of HPV infection - the interaction between the capsid protein of HPV (eg L1) and the membrane of cells at the basal layer of the epithelium [32]. The viral particles are thought to bind to another component of the cellular membrane. E6 and E7 oncoproteins have been found to play a key role in the cervical cancer carcinogenesis by altering the immune-response-related pathways and cellular transformation [32]. E6 and E7 are found to deregulate fundamental cellular evens, such as cell cycle, apoptosis, DNA repair, senescence, and differentiation. They also facilitate damage to DNA and the progression towards malignancy [32].

Figure 1-8: The structure of HPV and the integration with epithelial cells.



Reproduced from the 2008 Nobel Prize official website (*Nobelprize.org*)[31]

Epidemiological evidence

A systematic review and meta-analysis [33] published in 2008 suggested a strong and consistent association between persistent HPV DNA and CIN2-3/HSIL+. Forty-one studies (36 from Europe and North America) of over 22, 500 women were included in the review. The RRs (relative risks) ranged from 1.3 (95% CI: 1.1–1.5) to 813.0 (95% CI: 168.2–3229.2) for CIN2-3/HSIL+ compared with <CIN2-3/HSIL+; 92% RRs were above 3.0. The variation in the magnitude and precision of RRs was influenced by the reference group - uninfected women, women with mixed HPV infections, and women with transient HPV infections. The magnitude of association was stronger with a longer duration of infection (12 months), wider testing intervals, and the use of an HPV-negative reference group [33].

There are more than 100 types of HPV. Eighteen of these types are carcinogenic (HR HPV), (eg HPV types 16, 18, 26, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 73, and 82) [34]. The remaining genital types (LR HPV) (eg HPV types 6,11,42,43, etc.) are of low or no carcinogenic risk [34]. HR-HPV is estimated to cause 99.9% of cervical cancer cases, 90% of anal cancer cases, and 40% of external genital cancers cases (of the vulva, vagina, and penis) [34] [35]. It is possible for multiple HPV types (LR HPV and HR HPV) to be identified in one infected person. But the risk of developing cervical cancer with multiple HPV infections is not clear [4].

The means of HPV transmission currently known are: penile-vaginal intercourse, penile-anal intercourse, skin-to-skin genital contact (eg oral-genital, penile-vulvar, although this is less common than transmission through penetrative intercourse), and transmission to a new-born baby from the cervix of an infected mother (uncommon) [34].

1.2.4 Cofactors of HPV infection and cervical cancer

There are multiple factors influencing HPV acquisition and persistence as well as the development of cervical cancer. Three groups of cofactors are identified as playing an important role in the etiology and development of cervical cancer [36]. They are:

- environmental factors [36], including hormonal contraceptives, tobacco smoking, multiple sexual partners, and co-infection with other STI agents;
- viral factors [36], including viral load and viral integration;
- host factors [36], including hormones, genetic factors, and immune response.

Viral and host factors were discussed above in the section on HPV virology and immunology, and the evidence for environmental factors is mainly shown in this section.

The mechanism by which environmental factors influence cervical cancer development in terms of virology, immunology, hormone response and genetic susceptibility, etc is not clearly understood; the identified mechanisms are plausible rather than certain. Further studies are ongoing to explore stronger biological evidence of this mechanism.

The last decade experienced a rapid growth in epidemiological studies [3] [36] [37, 38] addressing the role of oral contraceptives, multiple lifetime sexual partners, smoking, etc. on the acquisition of HPV infection and the development of cervical cancer. Due to the increasing number of epidemiological studies, a series of systematic reviews and meta-analyses [39-43] were conducted to summarise the pooled effects, which provide sound evidence in this area.

Since 2005 the International Collaboration of Epidemiological Studies of Cervical Cancer (ICESCC) has conducted a series of collaborative reanalyses (meta-analysis) regarding the role of environmental factors in cervical cancer [39-42]. It provides solid evidence in terms of an epidemiological perspective. The environmental cofactors related to HPV infection and cervical cancer are listed and discussed below.

Sexual behaviours (the lifetime number of sexual partners, age of sex debut, condom use)

ICESCC organised a collaborative analysis from 21 epidemiological studies [39], assessing the role of lifetime number of sexual partners and age at first sexual intercourse on cervical cancer. Half of the studies were from less developed countries. The meta-analysis included 15,461 women with cervical cancer and 29,164 controls. The RRs was 2.78 (95% CI: 2.22–3.47) times higher among women who had had 6 or more lifetime sexual partners compared with those who had had only 1 partner. The RRs was 2.05 (95% CI: 1.54–2.73) times higher among women whose first had sexual intercourse at 14 years old or under compared with those aged 25 years or older. The adjustment included age, study, reproductive factors, and sexual behaviours [39]. But HPV status cannot be obtained from all included studies, which, to some extent, undermines the strength of the association.

There are no consistent results to suggest whether condom use is associated with the risk of HPV infection (either increased or reduced). But recent data showed that consistent condom use reduces the risk of male-female genital HPV infection. Further, condom use is associated with regression of dysplasia [4, 28].

Reproductive factors (number of full-term pregnancies, age at first full-term pregnancy)

ICESCC conducted a meta-analysis in 2006 [41] of 16,563 women with cervical cancer and 33,542 controls in order to assess the association between reproductive factors and cervical cancer. Twenty-five epidemiological studies were included, half of which were from less developed countries (such as Nigeria, Philippines, Mexico, Thailand,etc) [41]. Associations were found between the number of full-term pregnancies and age at first full-term pregnancy and cervical cancer. The relative risk (RR) was 1.76 (95% CI: 1.53–2.02) for 7 or more full-term pregnancies compared with 1–2. The RR was 1.77 (95% CI: 1.42-2.23) for those aged under 17 years at their first full-term pregnancy compared with those aged 25 years or under [41]. The adjustment on the potential confounding included study, age, lifetime number of sexual partners, and age at first sexual intercourse.

The hypothesised mechanisms include: high concentrations of oestrogen and progesterone during pregnancy, leading to columnar epithelium ectopy (equamo-columnal), thus increasing the likelihood of exposure to HPV infection [36]; hormonal changes during pregnancy may accelerate cervical carcinogenesis (by enhancing gene expression)[36]; and immune depression caused by pregnancy, which may affect the effectiveness of the immune response in clearing HPV infections [36].

HIV infection

High-risk and multiple HPV types are more prevalent among HIV-positive people, especially among men who have sex with men (MSM) [37, 38]. Biological studies suggest that immune response is involved in the clearance of HPV infections [32]. Epidemiological studies found that the incidence of cervical cancer was higher in immune-compromised individuals than normal ones[32]. However, it is unclear whether it is the immunosuppression caused by HIV infection or the higher-risk sexual behaviours among HIV-infected people that increase the risk of HPV infection acquisition and persistence.

Long-term use of oral contraceptive pill (OCP)

Epidemiological studies [40, 43] have shown that the long-term (more than 5 years) use of OCP is associated with HPV infection. A systematic review and meta-analysis in 2003 [43], including 28 studies (16 of developed countries) with 12,531 women with cervical cancer and 26,711 controls, reported 5 or more years' use of OCP led to a 1.6 times increased risk of cervical cancer compared with those who had never used an OCP (RR=1.6, 95% CI:1.4–1.7). The relative risks were identified as similar for women with ACC and SCC. Another collaborative analysis (ICESCC) in 2007 of 24 studies worldwide (half of which were from less developed countries) confirmed the association [40]. The analysis included 16,573 women with cervical cancer and 35,509 controls, and confirmed that 5 or more years' use of OCP increases the risk of invasive cervical cancer to 1.90 times that of those who had never used OCP (RR=1.90, 95% CI: 1.69–2.13); while the risk declined when use stopped [40]. The possible mechanism [36] of the effect of oral contraceptives is that oestrogens or progestagens enhance HPV gene-expression in the cervix through hormone response in the viral genome and hormone receptor route.

Although long-term OCP use is responsible for HPV infection (1.5% of Chinese women use OCP)[2], tubal ligation and the use of intrauterine contraceptive devices are the most commonly used contraceptive methods in China, and neither has been found to be associated with HPV infection [17].

Smoking

Smoking is another risk factor for HPV infection, as it is thought to suppress immune function, reducing the immune response in the cervix as well as affecting the metabolism of female hormones [36]. The tobacco-related carcinogens are also thought to damage gene expression in the cervix [36]. Epidemiological studies [42] confirmed the association between tobacco smoking and cervical cancer. A meta-analysis (ICESCC) of 23 studies (half from less developed countries) including 13,541 women with cervical cancer and 23,017 controls in 2005, reported that increased relative risks of SCC were identified as 1.6 times higher among current smokers than among those who had never smoked (RR=1.60, 95%CI: 1.48–1.83) [42]. However, an association between smoking and ACC was not found. No clear risk trend was found from when smoking ceased. However, due to heterogeneity between studies as well as the potential confounding effect of HPV infection status, the risks of smoking in relation to cervical cancer and the worldwide burden still need to be accurately explored and quantified.

Nutrition

A 2005 review [44] examined the potential role of diet and nutrition in cervical cancer. It included 33 studies in all, but 2 studies were conducted in developed countries. The evidence was classified as convincing, probable, possible, and insufficient based on the World Cancer Research Fund and American Institute for Cancer Research, taking account to the strength of both epidemiologic studies and mechanistic or laboratory evidence [44]. There was no convincing evidence that diet and nutrition played a role in cervical carcinogenesis. There is a possible protective effect [44] of certain diets on HPV persistence, principally those diets rich in fruits, vegetables, vitamins C and E, beta-and alpha-carotene, lycopene, lutein/zeaxanthin, and cryptoxanthin. The probable protective effects [44] of diets on cervical cancer pertain to diets rich in folate, retinol, and vitamin E, and possibly vegetables, vitamins C and B12, alpha-carotene, beta-carotene, lycopene, lutein/zeaxanthin, and cryptosanthin [44].

The plausible mechanisms [36] here are that dietary factors may prevent HPV infection from progressing (transient to persistent). For instance, vitamins A and E regulate cell differentiation and proliferation. Vitamins C and E and other dietary constituents, acting as antioxidant nutrients, scavenge free radicals and oxidants, and could also modulate immune response and decrease viral replication and gene expression.

Summary

The association between environmental factors and cervical cancer has been explored through biological mechanisms and epidemiological studies. No confirmed mechanisms have been identified. In terms of epidemiological evidence, outputs from meta-analyses have provided more convincing evidence than individual studies. But the strength of the association is undermined by some uncontrollable factors. Regarding the ICESCC [39-42] study design, of the 25 epidemiological studies, 9 were cohort studies (all were in developed countries), 12 were population-based case control studies (10 were of developed countries), and the rest were hospital-based case control studies (all except two of which were in developing countries). It is said that the ICESCC [39-42] results could represent 85% of known published epidemiological studies worldwide and those not included due to their very small sample size had similar findings. But more prospective cohort studies are needed, especially in developing countries, to reduce the selection or recall bias that occurred in the case control studies. The heterogeneity between ICESCC studies [39-42] in the meta-analysis (which is difficult to avoid) is another potential factor undermining the findings relating to risks from environmental factors. Thus, the magnitude of the overall risk is uncertain and the possible subsequent cervical cancer burden and public health implications generated by the risk cofactors worldwide remain unclear.

1.2.5 HPV prevalence and type distribution in China

HPV prevalence in the general population

In 2012, a pooled analysis [11] based on 17 population-based studies of 30,207 women was conducted in China. The overall age-standardised HR HPV prevalence was 16.8%, and there was no significant difference between rural and urban regions. HPV 16 was the most common type in the survey, followed by HPV 58 and 52 [45-47].

The 17 cross-sectional population-based studies were conducted in five urban and nine rural regions of China (covering 9 provincial regions) from 1997 to 2008 [11]. The study locations included the Province of Shanxi, Guangdong, Liaoning, Jiangsu, Xinjiang, Henan, Jiangxi, and big cities like Shanghai and Beijing. The studies were supported by the Cancer Institute/Hospital of the Chinese Academy of Medical Sciences (CICAMS), in collaboration with the Cleveland Clinic (Cleveland, Ohio, USA), IARC, (Lyon, France), and PATH (Seattle, Washington, USA) [11, 48]. The participants were women who had never been screened for cervical cancer. They were tested by using Hybrid Capture Assay (HC2) and GP5+/6+ mediated PCR and PCR (MY09/11 primer) to detect the presence of HPV. [49] [45-47]. The HPV prevalence reported in China was largely dependent on the target population, study location, and the lab methodology (the DNA detection methods).

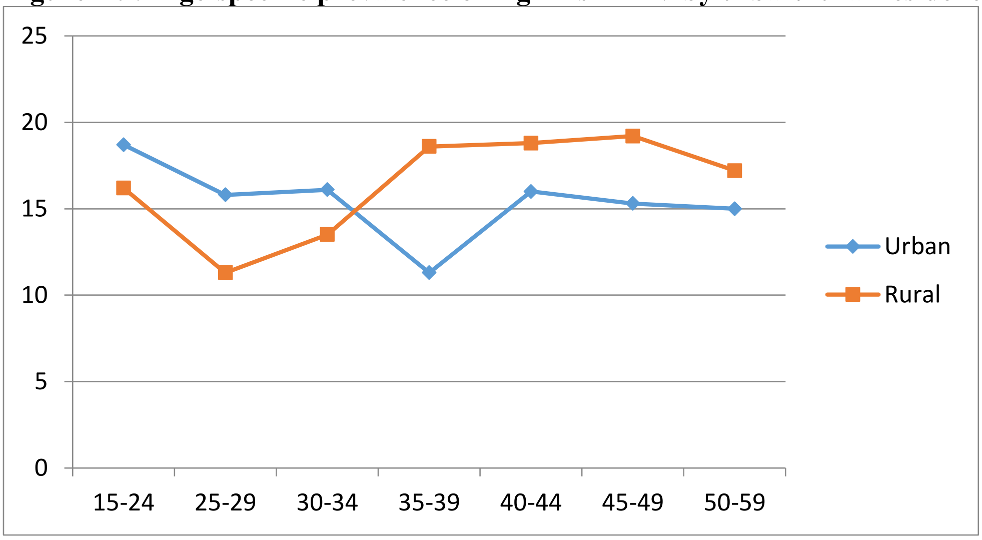
In 2007, a multi-centre study was conducted by the Chinese Academy of Medical Sciences to determine the distribution of types of HPV among women from seven areas in China [48, 50]. Around 1,200 women were included in the study; HR HPV DNA was detected by using the SPF10 LiPA25 version 1 assay, and histological diagnosis was used to confirm the type of invasive cervical cancer. In terms of SCC, HPV 16 (76.7%) and HPV 18 (7.8%) were the most common, together accounting for 84.5% of SCC, followed by HPV 31 (3.2%), HPV 52 (2.2%), and HPV 58 (2.2%). As for CIN 2/3, HPV 16, 58, 31, 52, and 18 were common, accounting for 68.7%, 12.5%, 7.4%, 6.5%, and 3.3% of cases respectively [50]. So, the two HPV vaccines would theoretically prevent 84.5% of SCC and 72% of CIN 2/3 for Chinese women. The results were similar those produced by the WHO report. The HPV 16/18 prevalence among women with normal cytology was 2.3%; it was 31.9% in women with low-grade lesions, 45.7% in women with high-grade lesions, and 71.0% in women with cervical cancer [2].

The HR reported HPV prevalence in China was higher than in the WHO report (12.2%), which was from five cancer registries a decade ago. This may be explained by the population and the time period selected. A systematic review on the HR HPV prevalence conducted by IARC in the WHO report included studies on Taiwan and Hong Kong [2] and did not include all the literature pertaining to mainland China. To avoid bias, Taiwan and Hong Kong studies have been excluded in this review due to their different cancer registry system and preventive strategies. The WHO report of 2010 updated previous Chinese data from 2002[2]. The HR HPV prevalence was similar to that in southern India (16.9%) [51], but higher than in many other low-resource countries in Asia, such as Thailand (3.9–9.1%) [52], Vietnam (1.6–11.4%), [52] and Pakistan (2.8%) [53]. Mongolia has a substantially higher HR HPV prevalence than most of Asia, at 35% [11].

HPV prevalence in different age groups

With regard to the age-specific prevalence of HR HPV, two Chinese studies (a pooled analysis of 17 studies [11] and a multi-centre study [54]) reported their results in terms of different regions. Only one peak was identified in high-risk HPV prevalence from 15–59 year old women in urban and rural residence. The peak was observed in urban women at age of 15–24 while in rural women at age of 35–49 [11]. Figure 1-9 shows the trends. However, two peaks were found in the HR HPV prevalence, one in the under-25 age group, and the other in the 40–44 age group [54]. Among four regions selected for the study, Shanghai had a relatively high overall prevalence of HPV (HR and LR) while a lower overall HPV prevalence was found in Xinjiang [54] (Figure 1-10).

Figure 1-9: Age-specific prevalence of high-risk HPV by urban/rural residence

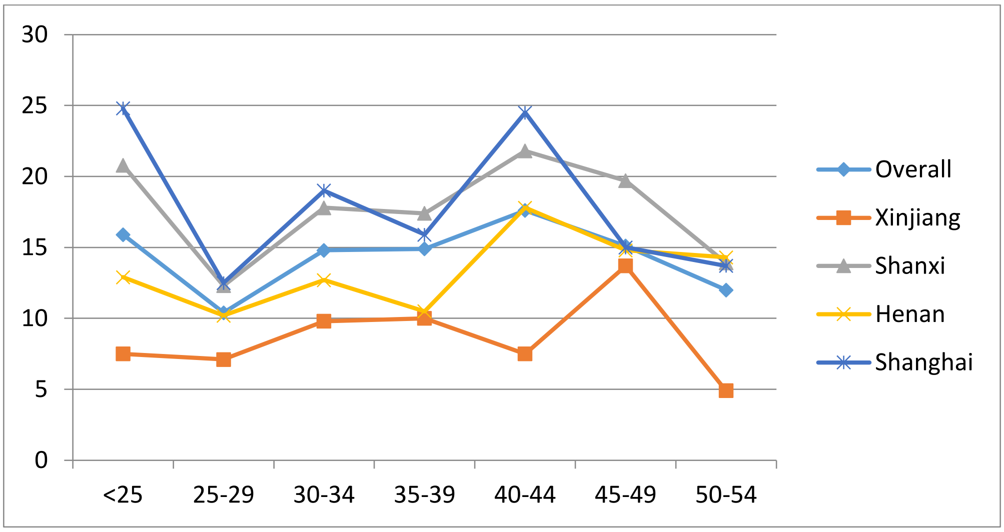


Reproduced from *Prevalence of human papillomavirus and cervical intraepithelial neoplasia in China: a pooled analysis of 17 population-based studies. 2012* [11]

HPV prevalence in high risk groups

Female sex workers and HIV-positive men and women have a significantly higher prevalence of HR HPV in China [38, 55, 56]. A study in Zhejiang in 2012 involving 288 female sex workers (FSW) reported an HR-HPV prevalence of 66.7% among FSW. The most frequent HR HPV types are HPV 16, 58, and 52. Rates of cervical abnormalities of 20.8% were found among FSW [55]. A Hubei province study in 2012 reported a 36.5% HR-HPV infection rate and a 33.5% rate of multiple HPV infection in HIV-positive Chinese women. HPV 16, 52, and 18 were the types most frequently found among HIV-infected men and women [56]. A study carried out in Beijing in 2013 with 212 HIV-infected participants reported that a prevalence rate of 61.3% for anal HR-HPV was found in HIV-infected men who have sex with men (MSM), and 45.8% of MSM had more than two HPV types [38]. All the studies were cross-sectional, regional (more developed regions) research-based ones, and the reported sample collection and laboratory tests were performed by trained and experienced physicians in local CDC and hospitals, so the data should have been accurate. However, the study design and the target population limited the representativeness of the results.

Figure 1-10: Age-specific overall HPV prevalence in four regions of China in 2006-2007



Adapted from figures in *Prevalence of type-specific human papillomavirus and pap results in Chinese women: a multi-center, population-based cross-sectional study* [54]
The four regions are from West to East China (Xinjiang, Shanxi, Henan and Shanghai)
Overall HPV prevalence includes both HR HPV and LR HPV.

Challenges in obtaining accurate data in China

There are some challenges in attaining accurate information about HPV prevalence in China. They are listed below:

Current cancer registries do not cover the whole population of China. Up until 2008, 41 cancer registries were available in China, covering 5% of the total population, including urban and rural regions[16]. The registries have expanded in the last few decades, but there are differences regarding the number of registries points, the number of people reached, and the quality of the data reported every year. Only nine cancer registries have continuous data (incidence and mortality rate) for the period 1989–2008[16].

Lack of national screening programme. No national screening programme exists to record data relating to cervical cancer, including HPV prevalence.

Selection bias in research-based studies. This arises from opportunistic screening and short-term (2–3 years) research-based studies. They are usually multi-centre studies, which are more representative than individual studies. But the target population may be confined to some specific areas of China where the prevalence (or incidence or mortality) is either high or low. HPV prevalence would be either overestimated in rural regions or underestimated in urban regions[48].

Selection bias of urban/rural sites. Researchers reported that no urban/rural difference in terms of HPV prevalence have been found. This may be due to the selection bias of urban sites and rural sites. The urban women were only from big cities, and the rural women came from high-burden counties[48].

HPV detection methods differ between urban and rural regions. GP5+/6+ mediated PCR detection is used in urban areas, and HC2 assay is used in rural areas. HC2 assay has higher sensitivity and is more standardised and easily controlled than PCR detection [48, 57].

The delay in reporting and lack of updates. The most recent data on HPV prevalence in China is from 2008, but the report became available only in 2012. Currently there are no data available on HPV from 2009–2013. The delay in reporting and updates may impede policy making as well as the implementation of prevention programmes.

1.2.6 HPV in China: Summary

The public health burden caused by HPV infection in China is high among the low- and intermediate-resource countries in Asia, but not the highest. The best estimate of HPV prevalence is 16.8% based on 17 studies of approximately 30,207 women. No time trend or geographical pattern has been identified until now. Since the source of the data is currently limited in terms of geographical regions, time period, study design, target population, and detention methods, it is possible that some trends or patterns might be found later when more accurate and reliable data is available. The challenges for establishing accurate information regarding HPV prevalence and the potential public health burden have been identified, and they mainly concern defects in the health system. But any national prevention approach will not be established in the near future and thus, the most possible and realistic way might be to combine research-based studies and current cancer registries together to get the reliable disease burden and achieve prevention goals. High-burden areas and high-risk groups might be the priority of the prevention strategy, but issues like how to access high-risk groups such as female sex workers pose another challenge.

1.3 Cervical cancer prevention

An ideal national cervical cancer programme should include four stages:[5]

- Primary prevention (education, HPV vaccination, male circumcision, etc.)[58]
- Secondary prevention (cervical screening)
- Diagnosis and treatment (follow-up of positive patients, treatment on precancer and ICC)[5]
- Palliative care (symptomatic relief, compassionate care, and involvement of the family and community)[5]

From the public health perspective, primary and secondary prevention are the most effective way to reduce incidence and mortality rates of cervical cancer at the population level, but the provision of vaccines or screening should not be non-organised and opportunistic[5].

The WHO has created a checklist [58] for cervical cancer prevention and control at the national level. A summary is adapted below. See Table 1-3.

Table 1-3: Checklist for cervical cancer prevention and control programme

Prevention and control	Target population
National policy or plan	General population
National guidelines	Health workers
Financial and technical resources	
National or local cancer registry	Women (incidence and mortality)
Health education and promotion programme	General population (males and females)
HPV vaccination	9–13 year old girls*
Cervical cancer screening with follow-up treatment	30–49 year old women
Referral system	Screening women (precancerous lesions and ICC) eg HPV triage in England. colposcopy referral indications: cytology>=low-grade lesions or HPV positive[59]
Monitoring system	Women at any of the stage of HPV vaccination, screening, and treatment

Adapted from WHO guidance [58]
* The age identified is generally based on western countries. The appropriate age to vaccinate girls varied across countries due to differences in age at sexual debut, and for China, it may extend to 13–15-year-olds [60].

1.3.1 Primary prevention

Primary prevention of cervical cancer mainly targets HPV infection and related risk factors and aims to prevent cervical cancer. It includes: health education and awareness raising, intervention on behaviours posing a risk to health (smoking, risk sexual behaviours, etc.), and HPV vaccination.

Health education and awareness raising

As demonstrated by controls on tobacco smoking for lung cancer and campaigns for condom use for acquired immune-deficiency syndrome (AIDS) [61, 62], health education intervention can reduce the risk of disease and, accordingly, save lives. The risk reduction of cervical cancer occurs through raising awareness of HPV infection, using methods of protection in sexual activities, and avoiding high-risk sexual behaviours [63]. Raising awareness of early detection through cervical screening is also useful, especially integrated with prevention and appropriate treatment of precancerous lesions. This would help reduce mortality in low-resource regions like China, Middle and Far East regions, and sub-Saharan Africa, where other methods like HPV vaccination will soon cease to be affordable and manageable on a national scale. IARC estimated that health education and awareness raising would prevent the deaths of millions of women from cervical cancer [64, 65].

Targeting health risk behaviours

Condom use

Consistent condom use may reduce the risk of HPV infection and cervical cancer. The recent (2014) systematic review of eight longitudinal studies (two randomised control trials (RCT) and six cohort studies) reported that those who consistently used condoms had a significantly lower risk of HPV infection, a higher chance of clearing existing infections (eg hazard ratio (HR) =0.58, 95% confidence interval (CI): 0.35–0.97), and a higher chance of regression from high-grade CIN (eg HR=3.1, 95% CI: 1.4–7.1; OR=5.28, 95% CI: 1.68–16.62). Potential confounding factors include the number of sexual partners, history of STIs, and 'social desirability' (by which respondents provide answers which they consider to be the most socially desirable) in reporting the information on condom use.

Male circumcision (MC)

The mechanism through which circumcision might protect people against HPV infection is not well understood. One plausible reason is that the removal of the foreskin could minimise the chance of viral entrance, and the smaller mucosal surface would lead to less HPV infection and mucosal trauma [66]. A systematic review and meta-analysis of 21 studies (involving 8,046 circumcised and 6,336 uncircumcised men) suggested a significant association between MC and reduced genital HPV prevalence (odds ratio (OR) = 0.57, 95% CI: 0.42–0.77) [66]. Weak evidence from cross-sectional studies (only two were RCTs) and potential selection bias undermine the strength of the epidemiological evidence. Further, the impact of MC on the prevalence of HPV in women is equivocal. So, safe sex (protected sex and low-risk sex) is still one possible strategy by which sexually active people could prevent further HPV infections[6].

HPV vaccination

In 2006, the US Food and Drug Administration (FDA) approved the quadrivalent vaccine (Gardasil) for use against HPV 6, 11, 16, and 18; it is estimated to prevent 70% of cases of cervical cancer and 90% of genital warts cases [67]. In 2009, the bivalent HPV vaccine (Cervarix) was approved by the FDA for use against HPV 16 and 18 and is estimated to prevent 70% of cervical cancer cases [67]. Both of the vaccines have been proved to be tolerated and efficacious in large-scale clinical trials [68], but the burden of cervical cancer will be reduced only when uptake of the vaccines is widespread. Table 1-4 summarises the basic information on the two types of HPV vaccine.

Table 1-4: Summary of two types of HPV vaccine

		Gardasil (quadrivalent)	Cervarix (bivalent)
HPV types		6, 11, 16, 18	16, 18
Prevention of disease		70% cervical cancer, 90% anal cancer, 40% external genital cancer (vulvar, vagina and penis), 90% genital warts, CIN1, 2, 3	70% cervical cancer, CIN1, 2, 3
Potential recipients		Females and males, 9–26 years	Females 9–25 years
Efficacy	Protection of disease	96% for precancerous lesions, vulva and vaginal and genital warts	90% high-grade CIN 75% HPV 16, 18
	Duration of protection	5 years	8.4 years
	Cross-protection	46% for HPV 31	77.7% for HPV 31,45 6.4 years
Safety		One serious adverse reaction in 0.8% vaccine recipients vs. 1.0% placebo recipients	One serious adverse reaction in 5.3% vaccine recipients vs. 5.9 % placebo recipients
Administration		0,2, and 6 months	0,1, and 6 months
Coverage		82% in Belgium (2010), 71% Australia (2009), 63% in Norway (2011), 32% in the US (2010)	84% in UK(>90% in Scotland) (2009), 56% in Italy (2012), 33% in the US (2010)

Adapted from *Prevention of human papillomavirus (HPV) infection and cervical cancer in China: How does HPV vaccination bring about benefits to Chinese women?[1, 69]*

By 2010, over 120 countries in the world had approved one of the HPV vaccines (either Cervarix or Gardasil) [70], 62 of which have included HPV vaccination in the national immunisation programmes [70]. Table 1-5 presents these countries. Neither of the HPV vaccines has been licensed in China, although Phase III clinical trials had finished by the end of 2013 [71].

Table 1-5: Cervarix and Gardasil approvals worldwide by 2010

	Cervarix (bivalent) (110 countries)	Gardasil (quadrivalent) (120 countries)
America	Canada, USA, Mexico Argentina, Aruba, Brazil, Chile, Colombia, Costa Rica, Curacao, Dominican Republic, Ecuador, El Salvador, Guatemala, Guyana, Honduras, Jamaica, Nicaragua, Panama, Peru, Surinam, Trinidad and Tobago, Uruguay	Canada, USA, Mexico Aruba, Bahamas, Barbados, Bermuda, Cayman Islands, Costa Rica, Curaçao, Dominican Republic, El Salvador, Guatemala, Honduras, Jamaica, Nicaragua, Panama, Puerto Rico, Trinidad/Tobago Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, Peru, Uruguay
Europe	EU (27)*, Iceland, Switzerland Albania, Armenia, Azerbaijan, Belarus, Bosnia, Croatia, Georgia, Kazakhstan, Macedonia, Moldova, Russia, Serbia, Ukraine	Albania, Austria, Belarus, Belgium, Bosnia, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Herzegovina, Hungary, Iceland, Ireland, Italy, Latvia, Liechtenstein, Lithuania, Luxembourg, Macedonia, Malta, Montenegro, Netherlands, Norway, Poland, Portugal, Romania, Russia, Serbia, Slovakia, Slovenia, Spain, Sweden, Switzerland, Turkey, UK, Ukraine
Africa	Burkina Faso, Congo, DRC, Gabon, Ghana, Ivory Coast, Kenya, Mali, Namibia, Nigeria, Senegal, South Africa, Tanzania, Uganda	Botswana, Burkina Faso, Cameroon, Central African Republic, Chad, Congo (Brazzaville), Cote d'Ivoire, Equatorial Guinea, Ethiopia, Gabon, Guinea (Conakry), Kenya, Malawi, Mali, Mauritania, Mauritius, Namibia, Nigeria, South Africa, Tanzania, Togo, Uganda
Asia Pacific	Bangladesh, Cambodia, Hong Kong SAR, India, Indonesia, Japan, Macau SAR, Malaysia, Myanmar, Pakistan. Philippines, Singapore, South Korea, Sri Lanka, Taiwan, Thailand, Uzbekistan, Vietnam Australia, New Zealand	Bhutan, Georgia, Hong Kong SAR, India, Indonesia, Kazakhstan, Korea, Kyrgyzstan, Macau SAR, Malaysia, Philippines, Singapore, Taiwan, Thailand, Uzbekistan, Vietnam Australia, Fiji, New Zealand
Middle East	Bahrain, Egypt, Israel, Kuwait, Lebanon, Mauritius, Morocco, Oman, Saudi Arabia, Tunisia, Turkey, United Arab Emirates	Bahrain, Egypt, Israel, Jordan, Kuwait, Morocco, Pakistan, Saudi Arabia, Tunisia, United Arab Emirates

*The data were obtained from *Human Papillomavirus Vaccines: Current status and future prospects* [70], but I was unable to obtain further details of the EU countries approving Cervarix.

Adapted from the figure of *Human Papillomavirus Vaccines: Current status and future prospects* [70], which was reproduced with permission from GlaxoSmithKline and Merck.

HPV vaccine mechanism

The HPV vaccines use virus-like particles (VLPs), containing viral capsid proteins—the major one (L1)—of different virus types (6, 11, 16, 18) to induce an immune response. The DNA of the virus is not contained in the vaccine, so the virus cannot replicate through it.

Experiments on animals have proved that the vaccines invoke an antibody response, which is much stronger than the natural immune response due to the adjuvants used in the vaccines. The L1 antibody is expressed in the cervical mucus, immediately neutralising the virus. As the efficacy of the vaccines against the internalised virus is not well understood, the vaccines are considered to be more effective before sexual debut [4].

HPV vaccine efficacy and safety

<u>Efficacy</u>

The most recent systematic review and meta-analysis [72] invoved seven unique randomised-controlled trials worldwide of 44,142 females were conducted in 2011, assessed the efficacy and safety of the two vaccines. Evidence suggested that both the vaccines were most efficacious (75–95%), depending on which sub-cohorts were enrolled) against a 6-month persistent infection with HPV 16 and 18 [72]. Regarding CIN1+ with HPV 16 and 18, the efficacy was 57–98% and 50–90% for CIN2+. Per-protocol population cohort (vaccine HPV type naive) tended to have higher efficacy than the intention-to-treat cohort (regardless of HPV status in the enrolment) [72].

The vaccines provide 100% protection against HPV 16 infection over 17 months and 94% after 3.5 years [4, 73]. In terms of precancerous lesions, vulval and vaginal cancer, and genital warts, a Phase Ш clinical trial of 17,000 women showed that for unexposed (to relevant HPV types) women, the efficacy of the quadrivalent vaccine is over 96% [74]. Phase Ш clinical trials also showed that the efficacy of the bivalent vaccine was over 90% in preventing high-grade cervical lesions and over 75% in preventing persistent infection (HPV 16 and 18) [74]. But so far the clinical trial studies do not have strong evidence for protection beyond 5 years – although the period of protection is likely to be much longer. It is estimated that the duration of protection for the bivalent vaccine is 8.4 years, and 5 years for the quadrivalent vaccine [34, 74]

The efficacy of HPV vaccine for different stages of dysplasia and ICC has to be available until 2020 due to the long-term development of cancer and very rare incidence [4]. However, some preliminary findings reported the efficacy in some high-income countries where HPV vaccines have been introduced for 4-5 years, such as Australia [75], Scotland [76] and Denmark [77]. The results showed 48% reduction in CIN3 in the quadrivalent vaccinated group in Australia [75], 29%, 50% and 55% of reduction in CIN1, 2, and 3 respectively in bivalent vaccinated group in Scotland [76] and 44-73% reduction of CIN2-3 in vaccination cohorts in Denmark [77]. Further, as neither all HR-HPV nor already present HPV infection are protected by the vaccines, implementation of cervical screening needs to be continued, but HPV vaccination offers the prospect of less intensive screening - the intervals between screening tests could potentially be widened.[4].

<u>Cross-protection</u>

Both the vaccines provide cross-protection against other HPV types. It is inferred that there are some phylogenetic similarities between L1 genes of the vaccines and other types. The bivalent vaccine is found to have 59.8% and 77.7% efficacy with HPV 31 and HPV 45 respectively for up to 6.4 years [29].

There is a possibility that if natural competition exists among HPV types, HPV type replacement (strain-replacement) would occur after vaccination. However, HPV 16 and 18 are the dominant types in the development of cervical cancer; other HPV types would carry a lower risk of developing cancer and in turn have fewer implications for public health [29].

<u>Adverse effects</u>

The most common adverse event seen in trials of HPV vaccination has been local discomfort at the injection site, including pain, swelling, and redness, headache, and low-grade fever, but this is usually of short duration. People who received the bivalent vaccine were more likely to report these local symptoms than those who received the quadrivalent vaccine [74]. In terms of serious adverse reactions, the most commonly reported was abnormal pregnancy outcomes[72]. However, there was not a significant difference in vaccine-related serious adverse events between the vaccine and control groups[72].

Health impact of HPV vaccines

Vaccine coverage, efficacy, and duration of protection are expected to influence the health impact of HPV vaccines [78]. As HPV vaccines have only recently been introduced, the health impact cannot be directly observed. Thus, models have been used in high-, middle- and low-income countries [78] to predict the incidence reduction for cervical cancer and precancerous lesions (CIN2/3). The estimated cancer reductions of vaccine-related HPV types (HPV 6,11,16, and18 in Cervarix and Gardasial) vary from 43% to 98% in Asia [78], America, [78] and GAVI-eligible countries [79, 80]. This variation may be attributable to the different model estimations of cervical screening frequency, vaccine coverage, inclusion of boys, and vaccination age range.

Delivery of HPV vaccine

Age and gender

To achieve the maximum effectiveness of the vaccines, and due to their prophylactic nature, the target population for vaccination should be those who are not sexually active. While the median age of sexual debut varies across different populations, most countries recommend girls aged between 10 and 14 years should take the HPV vaccine[74].

HPV-related burden is low among males and due to the efficacy and price of the vaccines, adolescent boys were not considered as the target population in most countries. However, the vaccination has been introduced in the all the states in US [81] and Australia [82, 83]. Studies showed HPV infection would be much more reduced by further increasing the vaccine uptake of girls rather than including boys in the programmes [29]. But if the coverage amongst girls is less than 50%, involving boys in the programmes may be cost-effective [29]. Involving boys in the vaccination programmes also offers some advantages to both men (particular high risk group, eg MSM) and women in the prevention of genital warts, oral cancer, and anal cancer, as well as providing herd immunity benefits to men's female partners [74].

Delivery and administration

Several strategies of HPV vaccination have existed worldwide, and China needs to find one appropriate for its current conditions. Below are the potential strategies.

- national free programmes, adding to the existing national immunisation system or EPI system (ie UK, Australia, US, Singapore, Malaysia) [84]
- national semi-free programmes, in which recipients pay for a proportion (ie France, 35% no reimbursement) [84]
- programmes not covered by any health insurance (ie Hong Kong, Taiwan, Japan, Korea) [85]

In terms of delivery venue, the WHO recommended several possible vaccine delivery strategies: school-based immunisation programmes, EPI (Expanded Programme on Immunisation) campaigns, adolescent-friendly health programmes, and community-based sexual and reproductive health programmes (eg family planning). [34]. Most developed countries (Canada, UK, and Australia) [74] deliver the vaccine through school-based programmes (school-based health services can reach more adolescents than community-based ones), while in some developing countries where the school attendance among girls is relatively low, school-based services would not achieve this optimal benefit and coverage. Thus, further studies are required to explore which delivery strategies would be most feasible and achievable in developing countries.

The two vaccines are administered according to a standard protocol, which means the quadrivalent vaccine is given at 0, 2, and 6 months, and the bivalent vaccine is given at 0, 1, and 6 months [74]. The possibility of reducing the number of doses from three to two is being discussed, and the schedule will become more flexible. It is expected to greatly reduce the costs and simplify the delivery of the HPV vaccine[74], thus increasing the coverage accordingly.

Coverage

School-based HPV vaccination programmes have achieved high coverage in some developed countries. In terms of the three doses, the coverage is over 70% in Australia (71%) (Gardasil, the quadrivalent vaccine, is used in Australia) [86], higher in Belgium (83.2%)[29], and was even higher in the United Kingdom in 2013 (86.1% in England, over 90% in Scotland) (Cervarix, the bivalent vaccine, is used in the UK immunisation programme, against HPV types 16 and 18)[87]. But in the US, coverage is only 33% for the three-dose series (both types of HPV vaccines are currently used in the US)[88]. In Australia, the national school-based HPV Vaccination Program has been extended to males. From February 2013, both males and females aged 12–13 years will receive the HPV vaccine (the quadrivalent vaccine) at school [82].

Cost-effectiveness of the HPV vaccines

A number of studies have employed cost-effectiveness models to assess whether the intervention (HPV vaccination) combined with other prevention strategies (eg cervical screening) is cost effective [78]. These studies typically use cost-effectiveness ratios to express the results, and no global standardised ratios are available currently [78]. The commonly used parameters to calculate the ratios include GDP, quality-adjusted life years (QALYs), and disability-adjusted life years (DALYs); the ratios are expressed as Cost per QALY, or Cost per DALY [78] [89]. The threshold of GDP is widely used as the evaluation criteria: a strategy (eg HPV vaccination) which has a ratio less than the average per capita GDP is viewed as very cost effective, and less than three times GDP is viewed as cost effective [78] [89]. In terms of the cost-effectiveness of the HPV vaccination, a number of factors influence the results, including vaccine cost, efficacy, coverage, duration of protection, health impact and frequency of cervical screening [89]. But it is still difficult to assume that measures of cost-effectiveness (of the HPV vaccine or HPV vaccine plus cervical screening) truly reflect the affordability of national health care or social willingness [90].

Ongoing issues of the HPV vaccines

<u>The vaccine type:</u> 1) Three-dose vaccines to two-dose vaccines: the antibody response, cross-protection, and duration of protection with two-dose vaccines need to be explored further [29]. 2) Nine-valent vaccine: studies are ongoing to add nine HPV types (HPV31, 33, 45, 52, and 58) to the quadrivalent vaccine. Trials showed the vaccine may provide 90% protection against SCC [29]. 3) Therapeutic vaccines: this kind of vaccine intends to increase the T-cell immune response using viral vectors. But issues of safety and administration need to be studied further [29].

Regarding the need for the full coverage of the HPV vaccines, several factors must be considered.

<u>Disease burden</u>: the HPV vaccines aim to prevent cervical cancer as well as genital warts. Compared to other cancers (lung cancer) and communicable diseases (HIV), cervical cancer and HPV infection are unlikely to be a priority in a national cancer or communicable disease prevention programme.

<u>Natural history of the disease</u>: Unlike other vaccines which aim to prevent infectious disease (measles, smallpox, hepatitis B virus (HBV), etc.), cervical cancer is a chronic disease which takes a long time to develop, during which screening could play a role in prevention and accordingly lower the risk of getting cervical cancer. Thus, the government would probably delay the introduction of vaccines due to the existent screening programmes and their long-term effects.

Protection duration and efficacy: the protection mechanism is not well understood, and studies need to explore it further.

Cost-effectiveness and affordability: it would be a big financial burden for a large country such as China to afford whole population coverage for HPV vaccines.

HPV vaccination in China

Summary of HPV vaccines in China

HPV vaccines have not been licensed in China—although there is some availability of the vaccine in Hong Kong, Macau, and Taiwan—but Phase Ш clinical trials are ongoing. These involve the Gardasil (Merck) quadrivalent HPV 16/18/6/11 vaccine and the Cervarix (GlaxoSmithKline Biologicals, GSK) bivalent HPV 16/18 vaccine (Table 1-6). They have been working to investigate the safety and efficacy of HPV vaccination in Chinese women[91]. A randomised double-blind trail among 100 males and 500 females was conducted in China to evaluate the efficacy and immunogenicity of the quadrivalent HPV vaccine produced by Merk. It showed that high antibody levels of the four HPV types were observed and that the vaccine is well tolerated, highly immunogenic, and has no serious adverse effects [92].

There are two Chinese vaccine manufacturers developing HPV vaccines for licensure in China, starting in 2014. INNOVAC (name of a Chinese pharmaceutical company) has an HPV vaccine in Phase III clinical trials, and Walvax has an HPV vaccine that is about to go into Phase III clinical trials (Table 1-6). No further details of the HPV vaccines of the Chinese manufacturers are yet known. The clinical trials will take many years to conduct, because the endpoint of the trials is the presence of precancerous cervical lesions. (WHO has recognised that these clinical trials could be accelerated by modifying the clinical endpoint, making it instead is 6-month persistent HPV infection, but this endpoint has not been used in China yet.)

Table 1-6: Status of HPV vaccines in China

Status of HPV vaccine production in China	HPV vaccine companies	Phase III clinical trials	Endpoint for clinical trials
International companies	Merck(Gardasil)	Finished (2013)	precancerous cervical lesions (>=CIN II)
	GSK (Cervarix)	Finished (2013)	precancerous cervical lesions (>=CIN II)
Chinese companies	INNOVAC	Ongoing (2014)	precancerous cervical lesions (>=CIN II)
	Walvax	Plan to (2014)	precancerous cervical lesions (>=CIN II)

Data was obtained from APEC Conference in Beijing in 2014 [93]

The appropriate age for HPV vaccines in China

To determine the appropriate age for HPV vaccines, a Chinese multi-centre cross-sectional study [60] assessed the sexual debut of 11,852 women aged from 15 to 59 years in 2009. It found that 4.5% of rural and 10.8% of urban respondents aged 15–19 years had engaged in sexual activity. In the 20–24 age group, 62.2% and 44.4% of rural and urban women reported engagement in sexual activity. The study accordingly employed standard frequency calculation and cohort analysis by age and urban/rural residence to estimate the median age of sexual debut. It was 17 years old in the 15–19 age group and 19 years old in the 20–24 age group for both urban and rural women [60, 94]

When the two age groups were split into students and non-students, the prevalence of sexual activity was significantly different. In the 15–19 age group, 23.1% versus 0.6% of rural participants (non-students versus students) and 38.8% versus 4.0% of urban participants (non-students versus students) had experienced sexual activity [60]. In the 20–24 age group, more pronounced difference were found: 71.7% difference (non-students versus students) for rural women and 46.7% difference for urban women (non-students versus students) [60]. Thus, finally, the study suggested that HPV vaccination would better starting between the age of 13–15 years, because of the potential earlier age of sexual debut among non-student women as well as the downward trend in the age of sexual debut [60, 94].

Lessons from Hepatitis B virus (HBV) *vaccination in China*

There has been a long time between the introduction of the HBV vaccine and full coverage via a free vaccination service in China—approximately 20 years from 1986 universal neonate immunisation to the free neonate vaccination in 2005 [95, 96]. A rough estimate on the delay of universal vaccination programmes showed that 64.000 carcinoma cases, 2.131.000 chronic cases, and 8,524,000 chronic HBV carriers should have been prevented during the period, but were not because of the slow speed of implementation of HBV vaccine [96]. Based on the experience of the implementation of the Hepatitis B Virus (HBV) vaccination in China, the HPV vaccination should be introduced across the whole country as early as possible, otherwise excess morbidity and mortality caused by HPV will substantially increase the disease burden and, in turn, the financial burden of the government. As estimated, in developing countries, every 5-year delay of the HPV vaccination leads to more than 1.5 million deaths from cervical cancer worldwide [20]. In China, a 7-year delay (2006–2012), would lead to 380,000 new cases and 210,000 deaths within the female population who should have been vaccinated during this period [97].

Challenges to the implementation of HPV vaccination in China

There are several challenges and recommendations concerning the implementation of the HPV vaccination in China.

First, it is necessary to determine if cervical cancer (together with HPV infection) is currently a health priority amongst adolescents and adults in China in terms of disease burden. It is also important to discover whether the reported burden has taken into account the relevant factors of the variability and mobility of the Chinese population. If this is not done, selection and information bias may exist and the burden will not represent the national estimates. For example, lack of data from rural residents and immigrants to cities would lead to an underestimation of the disease burden, thereby delaying it being made a priority in the schedule.

Second, publicity and education need to be widely carried out as soon as possible. Evidence showed that women who have less HPV and cervical cancer knowledge and do not think they would be infected by HPV [98] are be more likely to worry about the quality and safety of HPV vaccine and have lower acceptability [91].

Third, in terms of the high cost of HPV vaccination, cost-effectiveness studies should be conducted in China to help the government make a finance plan. A study [91] conducted in 2010 in China has suggested it would be cost effective to have a cervical cancer preventive strategy combining screening and vaccination approaches together. It indicated strategies including vaccination would cost US$50–54 per girl vaccinated, but if costs rose to over US$54, there would be no need to include vaccination in the preventive strategy [91].

Optimal strategies of the HPV vaccination combined with screening should be studied further in China in different socio-economic areas. The affordability to the government and the distributional equity also need to be explored [99].

Fourth, the different priorities among diverse stakeholders are considered to be a potential impediment to implement HPV vaccination in China. The stakeholders include sexual and reproductive health, adolescent health, immunisation, and cancer prevention departments, which are such mixed groups that it is difficult to coordinate them all together. Plus, due to the delayed impact of the HPV vaccination (rather than the immediate impact brought by the measles vaccination), stakeholders need to make decisions regarding whether it is important to save lives now or in the future [99].

Finally, a persistent HPV infection of over 6 months, recommended by WHO, should be used as the efficacy endpoint for Phase III clinical trials in China rather than precancerous lesions (CIN 2+). The current efficacy endpoint in China (CIN 2+) would require a large amount of people to reach an acceptable sample size, as well as long-term observation (maybe over 10 years) to get the relevant data. If the WHO-recommended endpoint is not used, the approval process in China will be delayed another 10 years (2016 will mark 10 years since the introduction of the vaccine [96].

Expanded programme on immunisation in China

Current immunisation programmes in China

The Expanded Programme on Immunisation (EPI) was established in 1978 in China [100]. By 1995, China had achieved its universal childhood immunisation goals of over 85% coverage in the whole country from the provincial level to county and village levels [100]. In 2007, the expansion of the National Immunisation Plan (NIP) [100] was announced by the central government, and a few vaccine-preventable contagious disease were added. The number of the NIP vaccines had increased from 6 to 14 by 2014, contributing to the prevention of 15 contagious disease [100] (Table 1-7). The primary goals of the NIP is to:

- maintain poliomyelitis-free status
- eliminate measles by 2015
- reduce chronic hepatitis B infection

Two categories of vaccines are provided in China [100]. The first category of vaccines are provided free of charge by the government for the citizens; they include NIP vaccines and vaccines for emergency immunisation. The second category of vaccines are paid for by citizens themselves and provided on a voluntary basis (Table 1-7).

Likely future scenarios of HPV vaccine availability in China

The Merck and GSK vaccines will be most likely licensed first in China, but they would be put into market as self-pay vaccines based on the current EPI and NIP systems in China, in line with the priority of vaccine-preventable disease of the government. Even after HPV vaccines are licensed by Chinese manufacturers, they will not likely be automatically made available free of charge to the target girls and boys (at no cost to their parents) in the EPI and NIP systems. To implement the HPV vaccines in China at no cost or low cost to the potential recipients, an agreement has to be reached between the National Health and Family Planning Commission (NHFPC) and the Ministry of Finance. GAVI purchases HPV vaccines for GAVI-eligible countries, but China is not eligible in terms of the economic conditions and potential affordability. Plans for the prequalification of the Chinese HPV vaccines are not detailed on the official NHFPC website or even known by the public via mass media. To speed up the licensure of HPV vaccines in China, a faster endpoint for clinical trials may be viewed as a way to help the Chinese manufacturers as well as the policy makers and other stakeholders.

The potential strategy of HPV vaccines in China

Several strategies of HPV vaccination exist worldwide, and China needs to find one appropriate for its current condition. It would not be realistic to implement a vaccination programme free of charge in the whole country due to the affordability to the government and logistical issues. The programme would initially target high-risk people (those who are more likely to have unsafe sex, be unaware of protection methods, start early sex, etc.) and high-burden cervical cancer regions. For example, Xinjiang Uyghur Autonomous Region, where the illiteracy rate is 29% (compared with a national average of 4.1% in 2010) and 93% of residents live on $1.0 or less per day, there is a very high prevalence of cervical cancer (622/100.000 women in 2007) [20].

Table 1-7: China expanded NIP vaccines and target diseases since 2007

NIP Vaccines		Target diseases	
Child immunisation plan vaccines			
1	Hep B	1	Hepatitis B
2	Bacilli Chalmette Guérin (BCG)	2	Pulmonary Tuberculosis (PTB)
3	OPV	3	Poliomyelitis
4	Diphtheria and Tetanus toxoid with a cellular Pertussis vaccine (DTaP)	4	Pertussis
5	Diphtheria and Tetanus toxoid Vaccine (DT)	5	Diphtheria
		6	Tetanus
6	Measles Containing vaccine (MV)	7	Measles
7	measles, mumps and rubella (MMR)	8	Rubella
		9	Mumps
8	Japanese encephalitis vaccine (JapEnc)	10	Japanese encephalitis
9	Meningococcal A vaccine (Men A)	11	Epidemic cerebrospinal meningitis DCSM
10	Men AC		
11	HepA	12	Hepatitis A
Vaccines for susceptible people			
12	Haemorrhagic fever vaccine	13	Haemorrhagic fever
13	Anthrax vaccine	14	Anthrax
14	Leptospira inactivated Vaccine	15	Leptospirosis

Reproduced from *The National immunisation plan: China 2010 [100]*

1.3.2 Secondary prevention (cervical screening)

Evidence [19] [101] has proven that cervical screening offers a protective impact on the reduction of cervical cancer incidence and mortality. A recent (2013) systematic review and meta-analysis [101] of 24 studies reported cervical screening has substantial protective effects when screening is offered to women aged 30 years and over and at intervals of 5 years or less intervals. Due to the heterogeneity of different studies, the review reported its findings based on the study design and screening method. An Indian RCT in 2009 including 131,746 women suggested a single lifetime screening could significantly reduce the risk of mortality and incidence compared to non-screening. The RR for mortality was 0.65 (95% CI: 0.47–0.90), and was 0.56 for incidence (95% CI: 0.42–0.75)[102]. A UK cohort study in 1996 including 116,022 women showed cytology screening significantly decreased the risk of being diagnosed with CC compared with non-screening (RRs 0.38, 95% CI: 0.23–0.63)[103]. The findings were also confirmed by 12 case-control studies involving 4,800 cases and 18,000 controls. (OR 0.35, 95% CI: 0.30–0.41). However the heterogeneity statistics were significant and can be explained by the inclusion of diverse countries (Colombia, Mexico, Italy, Sweden, South Africa, Japan, etc.) [19]

Cervical screening methodology

There are several screening methods (Table 1-8) available for both developed and developing countries, although the cervical screening is almost non-existent at the national level in resource-constrained countries.

Table 1-8: Major characteristics of the screening methodologies for cervical cancer

Characteristics		VIA*	Cytology testing		HPV DNA test
			Pap smear	LBT	
Sensitivity		50.0–89%	50–80%	70–85%	83–100%
Specificity		67–90%	86–90%	78–90%	65–99%
Quality control		No standardised	Second reader		Repeat test
Result		Subjective	Subjective		Quantitative
Training		Weeks (eg 3–14-day training courses)	Months		Weeks
Personnel & technique requirement		Lower personnel and lab requirements	Human errors lead to low sensitivity		Can be self-sampling
Cost 2010	Overall	Inexpensive	Expensive (more for follow-ups)		Expensive
	CN¥/test per person	10	30	200	300
	US$/test per person	1.5	4.5	30	45
	Per 1,000	$1,500	$4,500	$30,000	$45,000
	Per 1 million	$1.5 million	$4.5 million	$30 million	$45 million
Suitable regions		Low-resource	High- and low-resource		High-resource

Currency exchange rate was US$1=CN¥6.623 on 31 December 2010 (Bank of China)
*VIA: Visual inspection with acetic acid; LBC: Liquid-based testing
Data was obtained from three papers [69, 97, 104]

VIA: Visual inspection with 3–5% acetic acid (VIA) is commonly used in low-resource areas, as it is an inexpensive, simple test. The examiner uses acetic acid on the cervix, and when the testing areas turn white, the result is positive. It requires a low level of infrastructure and can be performed by a wide range of personnel. Its sensitivity and specificity are relatively low in comparison with other screening methods shown in Table 1-8 [105]. One meta-analysis indicated that region, capacity of screener (health worker, nurse, or physician), place of screening, study period, and size of study population had no effect on VIA accuracy, which suggests that VIA is reliable [106].

Cytology testing: Cervical cytology testing (ie the Papanicolaou (Pap) smear and liquid-based test) is also a commonly used cervical cancer screening method in both high- and low-resource areas. The Pap smear aims to detect cytological abnormalities and to classify the cancer risk (PAP I–IV). The classification is now used together with epithelial dysplasia or CIN 1/2/3 to present the level of abnormalities of cervical cells in terms of cytology and histology. Table 1-8 shows the classification based on different methods. The advantage of the Pap smear is its overall high specificity. However, its sensitivity is low [107] (Table 1-8). Low sensitivity leads to a great many false negative results and requires the need for frequent screening. Human errors in sampling and interpretation (the specimen is stained and inspected by cytologists for abnormalities) lead to the low sensitivity of the Pap smear [4, 107]. Liquid-based testing has higher sensitivity and lower specificity compared to the Pap smear. The results of the liquid-based test are easier to read, and HPV can be tested in the residual specimen when cytological abnormalities are found [107].

HPV test: The human papillomavirus test (HPV DNA test) is used to identify high-risk HPV. Its sensitivity and specificity are shown in Table 1-8 [105]. HPV testing has been shown to have 30–40% higher sensitivity than cytology but lower (5–10%) specificity for detecting high-grade lesions[108].

It has been found that when combined with cytology, ie Pap testing, the HPV test can attain nearly 100% clinical sensitivity and nearly 93% specificity in women age 30 years or older [107]. Unfortunately, the test is expensive, requiring advanced technology to perform, so it could not be used widely in low-resource areas. The advantages of the HPV test compared with cytology are as follows: the process can be completely automated; it has quality-control procedures; it can be performed by self-sampling; it has a higher sensitivity for detecting HSIL in women aged 30 years or older[105].

Screening interval

One recent (2014) study [4] used the Markov model to evaluate the effectiveness of 17 strategies for cervical screening. Varying the screening interval between one to three years (for Pap testing or combined HPV testing) does not have a significant impact on the risk reduction (all are over 70%) in cervical cancer incidence or mortality, compared with a non-screening policy [4]. Even having Pap testing once every 5 years would achieve a risk reduction of almost two thirds for cervical cancer [4]. The US Preventive Services Task Force recommended in 2012 [109] that the interval for cervical screening using cytology (Pap smear) should be three years for women aged 21–65 years, and five years for the screening combining cytology and HPV testing together. England assessed the screening interval for the use of HPV testing as the primary screening method and found that HPV test screening could safely extend the screening interval from 3 (cytology screening interval) to 6 years [110].

A study [111] on when screening should stop found that by the age of 65, 80% of the benefit of cervical cancer screening is achieved. By the age of 75, 3 days in life at the most would be lost due to the non-attendance for screening, and by the age of 80, it would be 1.5 days [111].

Screening coverage

From a public health perspective at a population level, greater efficacy would be achieved through targeting more women who have never had cervical screening than through offering more frequent screening to those women who have already been screened [112]. The UK has the highest screening coverage (approximately 80% with a 5-year interval). Even so, the significant reduction of incidence (estimated 35%) was not seen until 20 years after screening began (eg from 15/100,000 in 1986 to 8.7/100,000 in 2005 in England) [113].

The following provides information on cervical screening coverage in the UK [114]. In England in 2003, the coverage (<3.5 years from last test) was 71% among women aged 25–49, and 81% (< 5 years) among those aged 50–64. It gradually dropped to 77.5% among 50–64-year-old women (< 5 years) and remained generally the same for 25–49-year-old women (<3.5 years) at 71.5%. For the younger group (25–29 years) in England, the 3.5 year coverage was low, standing at 62.0% in 2013.

Scotland [115] has a similar cervical screening uptake to that of England. Three-year uptake was 71.2% among women aged 20–60, and 5-year uptake was 78.1% in 2013. The uptake among the younger group was 53.5% (3 years) and 55% (5 years) among women aged 20–24 years, and 66.2% (3 years) and 73.5% (5 years) for women aged 25–29.

Of the non-attendees, women with low socio-economic status account for the majority [3]. These women tend to have a higher risk of HPV infection and cervical cancer (because of a lack of sexual knowledge and awareness of self-protection) [3]. Thus, increasing uptake targeting of the non-attendees would reduce health inequalities to some extent.

Swedish studies [6] reported several methods—telephone invitations, interviews, and media promotion—that can be applied to increase the compliance rate in the cervical screening programmes. However, the use of such methods will be dependent on their financial affordability in local regions, as such management will as least triple the screening costs, based on experiences in Sweden.

Ongoing issues of cervical screening

Low screening coverage (especially in developing countries): There is evidence that at least 50% of cervical cancer worldwide can be attributed to the lack of cervical screening [116-118]. In most regions, including rural China, cervical screening is used as an opportunistic tool for cervical cancer prevention. Even in the US, 25% of women have not received cervical screening in the last 3 years [118].

Screening errors: It is estimated that one-third of cervical cancer cases are attributable to errors in Pap screening [117, 118]. Results are more accurate when Pap testing and HPV testing are combined, yet the high cost of this is not affordable in most developing regions.

Lack of follow-up for the screening: It has been found that the lack of follow-up screening and treatment leads to the occurrence of at least 12.5% of cervical cancer cases [118]. This problem is particularly prevalent in low-resource settings where a systematic cervical cancer prevention strategy has not been developed.

Cervical screening in China

National cervical screening programmes in China

The national health and family planning commission (NHFPC) has launched a free national breast and cervical cancer screening programme, targeted rural middle-aged women (35–59 years old) from 2009, covering 1,140 counties across 31 provinces in China. The accumulative total investment has reached 1.09 billion yuan, and 37.15 million rural women have been screened and 46,000 women diagnosed. In 2013, China invested 370 million yuan in conducting cervical screening for a total of 10.14 million rural middle-age women, thus the women were able to get early detection and early treatment (partly paid for by NRCM and insurance). An HPV screening pilot will be started by NHFPC for around 546,000 women in September 2014. The current available cervical screening methods are cytology screening and VIA, in urban and in rural areas, respectively. The colposcopy examination will be provided for women who have positive results from the gynaecological and cervical cytology examination (about 10%). The project has played an important role in reducing the disease burden, reaching the objective of early discovery, early diagnosis, and early treatment. (Data were obtained from NHFPC official website).

The NHFPC national screening programmes have brought about a great improvement in the primary care of women's cancers in China. The central government has made great efforts through the provision of financial and human resources to support the prevention of cervical cancer. The future plans of the NHFPC national programmes are not yet known, and their long-term effect and success largely depends on timely surveillance and follow-up treatment.

Cervical screening health impact

Available data suggest the mortality rate for cervical cancer dropped by 68% from the early 1970s (10.3/100,000) to early 1990s (3.3/100,000) in China, and this achievement was mostly attributable to the numerous organised cervical screening programmes in the rural regions of many provinces before the 1980s [18]. However, when China's market economic reform started in the early 1980s, public attention and interest turned towards high-profit industries, and, accordingly, funding for public health, including primary prevention (cervical screening) for cervical cancer, was no longer sufficient due to the profit-driven environment.

In the last decade, even though some sporadic cervical cancer control programmes have been implemented in many provinces in China, their effectiveness was not satisfactory (suggested by the mortality increased to 4.3/100,000 in 2008) [16]. Three main issues exist in the current cervical cancer control programmes in China. First, these programs are for a short period (3 years), and they are grant-supported in a few rural regions. If the grant runs out, the programmes stop. Second, these programmes were designed for research purposes to collect data on incidence and mortality or to conduct trials on screening methods. When the research finishes, the programmes stop as well. Third, screening effectiveness would be enhanced by the integration of health education and follow-up treatment [16, 97]. Yet, Chinese short-term research programmes are usually independent of a sustained screening provision, and do not involve the continued education and subsequent treatment of recipients – screening which is disconnected from appropriate treatment and follow-up tends to be ineffective [97].

Coverage of cervical cancer screening

There is not an established national screening programme for cervical cancer in China. The World Health Survey reported by WHO in 2003 indicated that the overall coverage of cervical cancer screening (by Pap smear) in China is 16.8% among women aged 18–69 and that the coverage varied in urban (21.5%) and rural areas (14.8%) [2]. It was a sample survey, and 2,036 women were selected through multistage cluster sampling. These women self-reported having received a Pap smear test during pelvic examination in the last 3 years [2].

Cervical cancer programmes in China

In 2006, China's government implemented a project to provide low-cost, low-technology screening - visual inspection with 5% acetic acid stain (VIA)/visual inspection with Lugol's iodine (VILI) screening to six counties in China. Now 42 clinical sites that provide screening services have been established in China (at least one clinical site for each province), and 3,500 women aged 30–59 have received screening at each site [17]. In 2009, China's government launched a cervical cancer screening programme for 10 million women living in rural China and provided visual inspection or Pap smears over three years. However, the majority of the women who need to be screened do not have the chance, because 70% of the whole population lives in rural areas - a total of 350 million women aged over 15 [2, 119].

Several cervical screening projects were undertaken from 1998 to 2008 by the Cancer Institute and Hospital of Chinese Academy of Medical Sciences (CICAMS) and Cancer Foundation of China (CFC), in collaboration with various international organisations. These international organisations included the Cleveland Clinic Foundation (CCF, Cleveland, Ohio, USA), IARC, (Lyon, France), PATH (Seattle, Washington, USA), GSK (Belgium), and the University of North Carolina (UNC, USA). Nearly 40,000 women were screened as part of these projects in four urban and ten rural areas of China, throughout nine provinces. For many women, it was probably the only occasion on which they received screening in their lifetime [17, 119]. These projects have explored a range of aspects of screening; rapid screening tests for HPV DNA detection, screening characteristic evaluation, health economics evaluation on screening programmes, population-based HPV prevalence, and HPV type distribution in urban and rural areas [17] (see Table 1-9).

Further, the Bill and Melinda Gates Foundation provided US$1.68 million from the Programme for Appropriate Technology in Health to implement a 5-year project (2003–2007), developing three biochemical screening tests [120].

Now three sets of cervical cancer screening are considered to apply to different regions of China. The optimal set of screening strategies is suggested in the developed regions, combining HPV-DNA testing with liquid-based cervical cytology, which might be the best screening model with sensitivity and specificity of up to 98% and 84%, respectively (79). However, such an approach is too expensive to implement nationally, and only a small number of women in non-deprived regions may be able to access it - for example, those in Shenzhen (US$7162 GDP per capita); the general method of screening is suggested in the medium-developed regions, combining HPV-DNA testing with Pap smear test. The primary screening method in the most deprived regions of China, at present, is low technology - combining visual inspection with acetic acid (VIA) /visual inspection with lugol (VILI) (79). It costs only CN¥5 but has low sensitivity and specificity [95, 120]. Therefore, none of the three screening models currently in use in China meet the requirements exactly, and it is necessary to establish a cost-effective and affordable preventive strategy as well as HPV triage tailored to different geographical regions.

Table 1-9: Selected projects [17] on HPV and cervical cancer in China

Project Title	Location	Age (years)	Number	Year
Shanxi Province Cervical Cancer Screening Study	Shanxi, Beijing, Xinjiang, Henan, Shanghai	35–45, 35–50, 16–54	1,997 9,034 5,000	1998–1999, 2001–2002, 2006–2007
Prevalence Survey of HPV infection and cervical cancer	Shanxi, Liaoning Guangdong	15–59	2,226	2004–2005
Screening Technologies to Advance Rapid Testing	Shanxi,	30–54	9,057	2003–2007
HPV Type-distribution Study	N/A	20–86	1,234	2006–2007
Health Economics Evaluation	Shanxi, Jiangsu, Guangdong	30–59	15,750	2006–2008

1.4 Summary

Cervical cancer and HPV

Cervical cancer is ranked as the fourth most prevalent female cancer in the world, with 530,000 new cases and 275,000 deaths every year. China, as a large and heterogeneous country, contributes 14.2% of new cases and 12% of deaths to the annual global figures. The incidence rates in China are similar to those of developed countries (such as US and UK), but the lack of availability of national cancer prevention programmes and the ongoing upward trend in both incidence and HPV prevalence in recent years could lead to a greater public health and financial burden for the country. The current situation is mainly attributable to the social and economic transition ongoing in China, which produces a highly profit-driven environment, a growing gap between the rich and the poor, and delays in the implementation of a national health care system – a more public health approach is required if appropriate investments are to be made in cervical screening.

HPV vaccines

As one of the biggest research achievements in the recent years, HPV vaccines have the potential to prevent 70% of cervical cancer cases worldwide. More than 120 countries (both developing and developed countries) have implemented at least one of the HPV vaccines nationally throughout the five continents, and the meta-analysis of RCTs I previously described has confirmed the efficacy and safety of the two vaccines. The immediate effect is protection against 6-month persistent infections of HPV 16 and 18 (75–95%), and in the future, the efficacy should be 50–90% for CIN1+ and CIN2+. The efficacy studies are still ongoing. Although Phase III clinical trials finished in 2013 in China, the introduction of HPV vaccines to China has not been made a priority in health care. Two main obstacles to the vaccines are the unrealistic endpoint for the clinical trials (CIN2+) and the big financial burden caused by the large number of potential recipients (0.3 billion).

Cervical screening and prevention programmes

The cervical screening coverage reported in China is 16.8% - that is, available data (from 2003) indicate that 16.8% of women (aged 18-69) had had a smear in the previous 3 years. However, this was only a sample survey of 2,036 women. As I've indicated, all the other cervical screening programmes are mostly research-based and short-term (usually 3 years) screening initiatives, without subsequent education and treatment. Some issues need to be solved before implementing national screening programmes in China. First, HPV triage should be set up for women according to different geographical regions and socio-economic groups. Second, given the large and heterogeneous nature of China, the optimal path would be to first implement screening programmes in high-risk groups or high-burden areas. But some issues must first be addressed regarding how to access high-risk groups and how to ensure health inequity. Third, a complete cervical cancer prevention programme should be developed for China's current circumstances. This would include education, vaccination, screening, diagnosis, and treatment. It is critical for the success of cervical screening programmes to have adequate follow-up procedures (for example, colposcopy and treatment services) and an information infrastructure. At present these critical elements of successful screening are lacking. Further, as an essential part of the prevention strategy, education programmes would be critical, and thus, knowledge and beliefs of people regarding HPV vaccination and cervical screening should be assessed, providing the necessary information for any future policy.

A brief international comparison of cervical cancer prevention programmes in some countries involving cervical screening and HPV vaccination has provided in Table 1-10. It could be the background on which my following studies would be based and I hope it might also provide international experiences in cervical cancer prevention for future policies.

In this chapter I hope I have provided thorough background and contextual material for my thesis. Clearly there are significant challenges ahead if China is to develop an appropriate strategy for reducing the burden from cervical cancer. International evidence suggest that HPV vaccination needs to be an integral part of that strategy. Hence, in the following chapters I examine key implementation issues for HPV vaccination in China – focusing on knowledge, attitudes and beliefs in the population.

Table 1-10 A brief comparison of cervical cancer prevention programmes in selected countries

Region	Country	Cervical screening				HPV vaccination			
		Age (years)	Interval$ (years)	VIA/HPV test	Program type	Target population	Catch-up age	Coverage	Program type
Europe	France	>=25	3			11	12-20	25-29% (2012)	national
	Italy	25-64	3	HPV test	pilot	12	11-24	52% (2012)	national
	Norway	25-69	3			12		63% (2011)	national
	Belgium	25-64	3			12	13-18	82% (2010)	national
	United Kingdom	20-60/25-64	3			12-13	13-17	84-92% (2009)	national
America	United States	21-65	3	HPV test	national	11-12	13-26	32% (2010)	national
	Canada*	18-69	2	HPV test	pilot	9-14	14-26	50-86%	national
	Mexico	>=25	3	HPV test	national	11-13		67% (2010)	national
	Brazil	25-60	3	HPV test	pilot	10-11			pilot
Asia	China#			VIA	national				
				HPV test	pilot				
	India	18-69	3	VIA & HPV test	pilot				pilot
	Japan	>=20	1			13			national
	Korea	>=30	2						
	Singapore	25-69	3			9-26			national
	Malaysia	20-65	3			13	13-18		national
Oceania	Australia	18-69	2			12-13	13-26	71% (2009)	national
	New Zealand	20-69	3			12		40 (2010)	national
Africa	South Africa	>=30	10	VIA	pilot				
	Kenya			VIA	national				pilot
	Uganda			VIA	national	10			pilot
				HPV test	pilot				

*the screening age and interval varies slightly in different regions of the country
$the interval refers to those who have had 2-3 annual negative smears
China is lack of specific national cervical screening strategy (including HPV triage)
Data that has not been available is left blank in the table. Data was obtained from WHO report in 2014 *Human Papillomavirus and related diseases* [1]

2 Chapter 2 Literature review—Systematic review

2.1 Background

HPV vaccines have the potential to lower the incidence of cervical cancer, and they have been shown to be both biologically effective, and cost-effective from a health economic perspective when used with a combination of screening approaches in China [91].

Even when HPV vaccines are licensed in China, it is unlikely that HPV immunisation will be introduced free of charge to all because of the high financial burden associated with the large population in China (approximately 1.3 billion overall, with 200 million teenage girls), so it is likely individuals would have to choose to have the HPV vaccine themselves—a decision affected by individual perceptions of the HPV vaccine. Hence, before vaccination is initiated in mainland China, there is a need to understand the knowledge and acceptability that might affect the implementation of future HPV vaccination strategies.

English-language systematic reviews of knowledge and attitudes towards HPV vaccines have been mostly based in Western countries [67, 121, 122]. Seven studies carried out in mainland China [123-129] and written up in English are available on online databases (such as PubMed), but only one of these studies [124] has been included and the results synthesised in English-language systematic reviews. Two of the seven studies were English-language publications [125, 126] of existing studies in Chinese literature. Given the limited amount of English-language literature available from mainland China, there is a need to explore the Chinese-language literature to obtain a comprehensive understanding of knowledge of and attitudes towards HPV vaccines among Chinese populations.

In the past few years, great progress has been made in China towards providing full-text access to the large amount of information reported in Chinese-language academic journals. More than 1,000 academic periodicals biomedical and health journals are published, providing a large amount of health evidence that Western literature does not often report. Several databases [130] are available, for example, the China National Knowledge Infrastructure (CNKI), Wanfang, and Chinese Medical Current Content. There is a considerable literature relevant to the knowledge of and attitudes towards HPV infection and vaccination available online in many Chinese academic journals; many studies [124, 131, 132] have reported the findings from different regions of China. However, as yet there is no synthesis of the literature from across China, looking at all populations within the country.

Thus, there is a need to carry out a systematic review of the Chinese literature to synthesise findings from different regions of China.

The English-language papers provide some indicative evidence. Li's study [124]—the most influential study of HPV and vaccination in China—was the first one to comprehensively present knowledge of and attitudes towards HPV from a Chinese population, and is the only study included in the English-language systematic review [124]. The questionnaire used in this study has been widely adopted in other Chinese studies since 2008. It was a population-based study including 6,024 respondents, conducted in 2008 in 6 community clusters in three major cities and three rural areas [124]. The main findings of the study were that Chinese women had a poor knowledge of HPV (15.5%) [124], but a high acceptability of HPV vaccines (84.6%) (it did not mention the type of HPV vaccine) [124], although they have health and safety concerns. The percentage of knowledge varied between urban (21.6%) and rural areas (9.3%) [124]. The source of the HPV vaccine and its safety were the major concerns for women who were unwilling to be vaccinated. Women would, however, accept the HPV vaccine if it was offered by the government [124].

In order to more comprehensively understand what the Chinese population thinks and how they view the HPV vaccine, my review focuses on Chinese-language literature examining knowledge and attitudes of people in China about HPV infection and vaccination, ultimately aiming to improve understanding of how to implement HPV vaccination in China in the future. My synthesis of findings will likely be of interest to health policy makers, public health officials, and health practitioners seeking to introduce HPV vaccination uptake among the populations across China.

2.2 Aims and research questions

The aim of my systematic review is to better understand the knowledge of and attitudes towards HPV infection and vaccination in the Chinese population, as well as among health care providers in China.

My research questions are:

- What are the levels of knowledge about and attitudes towards HPV infection and vaccination among the general population, and among health care providers?
- Do awareness, knowledge, and attitudes differ by the age, gender, rurality, and ethnicity in China, and if so, in what ways?

- What are the predictors of HPV vaccination acceptability (such as awareness, knowledge, or attitudes in terms of cost concern or worries about safety)?

2.3 Methods

I followed standard systematic literature review methodology in carrying out my literature review: search strategy, study selection, quality assessment, data extraction, and data synthesis. I describe below how I carried out the survey and the rationale for why I chose the specific methods I did.

2.3.1 Search strategy

Databases

Two Chinese databases—the Chinese National Knowledge Infrastructure (CNKI) and the Wanfang database—were used, and searched from inception through to 30 November 2012. CNKI and Wanfang are the first and most widely used electronic databases in the academic field in China. Chinese researchers are trained to use both of these databases as soon as they begin academic work.

Chinese National Knowledge Infrastructure CNKI (http://www.cnki.net/) is the most comprehensive source of academic information in China and represents the Chinese equivalent of the "Web of Knowledge" or "Pubmed". It is the first internet publishing platform approved by the State Press and Publication Administration. Publications include secondary publications from traditional publishing methods, and first-time internet publishing, including text, images, audio, video, animation, online courses, and scientific data. Currently, CNKI has assembled more than 8,000 kinds of journal, nearly 1,000 newspapers, 180,000 Doctoral/Master's theses, 160,000 conference papers, 300,000 books, and more than 1,100 specialized databases. Doctoral/Master's theses, conference papers, and part of the database is secondary publishing, while periodicals, books, newspapers are first-time publications.

Based on detailed literature content indexing, the CNKI literature search provides title, author, keyword, abstract, and full-text search capabilities with exact match (displaying papers with exactly the same key words) and blur matches (displaying all the terms containing the key words); the literature search also provides a variety of intelligent sorting methods. Relevance ranking takes into account a variety of factors: citation relations, full text, and literature sources, to make results more relevant. "Times Cited" is sorted in ascending or descending order of publication date for each item; author index sorting is based on the amount of literature the author has published, the number of times that literature has been cited, and the impact factor of the academic influence of the author, and sorts the literature accordingly. I used keyword literature search with blur match in CNKI, and relevance ranking of the literature was applied: the literature was ranked based on the publishing time (those put in the front were the most recent ones).

Wanfang database Wanfang (http://www.wanfangdata.com.cn/) is another comprehensive database, which includes full-text papers published since 1998 from Chinese academic journals (the number of journals included is 4,529), PhD/Master's dissertation theses, and conference proceedings. It also provides title, author, keyword, abstract, and full-text search capabilities, as well as relevance ranking based on publishing time, impact factor, etc. The literature is ranked by the publication date, listed in descending or ascending order.

I considered using additional Chinese academic databases in my search, such as Chinese Scientific Journals Database (Weipu Database) and the Chaoxing Electronic Library. These two databases have unique features, but also have some weakness. The former is the oldest e-database in China, having been started in 1989, but it is not the most comprehensive one. It only includes journal articles and is not interface-friendly. Some recent journals are missing from Weipu, especially in the medical category. The latter database provides millions of e-books, 5 million papers, and over 80,000 academic videos. But the academic searching strategy (e.g. keyword searching) in the e-library is not developed. Based on the above reasons, these two databases were excluded from my search.

I used manual searches to go through relevant online journals in CNKI and the Wanfang database, scanned a reference list of identified studies, and included articles that met the inclusion criteria.

Search terms

MeSH search terms were applied to both Chinese databases included in my research (CNKI and Wanfang). I used the search terms (in the Chinese language) "HPV", "human papillomavirus" (renrutouliu bingdu), "HPV vaccination" (HPV yimiao), "HPV immunisation" (HPV mianyi) AND "knowledge" (zhishi), "perception" (renzhi), "awareness" (zhixiao), "attitude" (taidu), "acceptability" (jieshoudu), "will" (yiyuan), and "health behaviour" (jiankang xingwei). All the keywords used in the literature search are displayed in Table 2-1.

2.3.2 Study selection

Here I describe the criteria for eligibility and the selection procedure of the identified studies.

Inclusion criteria

I included all relevant study designs in the search strategy (although only cross-sectional studies with quantitative results were finally included in my review). The inclusion criteria are based on the following study characteristics.

<u>Article publication type</u>

- Peer-reviewed journal articles
- Conference articles
- Doctoral/master's dissertation theses

These are the main types of publication and are the types I was able to access through Chinese academic databases (CNKI and Wanfang). CNKI has three sub-databases based on these types, and Wanfang put them together in one database. They include almost all the literature published in the Chinese language.

<u>Study setting (but not restricted to)</u>

- Community-based setting,
- Hospital-based setting
- College- or school-based setting.

Based on the review of Western and Chinese literature in the preparation phase, it was found that studies of HPV knowledge were usually set in the hospitals, colleges or schools, and communities in cities or towns. But for included studies, restrictions on the study setting were not defined.

<u>Study location</u>

- Mainland China (because there are different health systems in Hong Kong, Macao, and Taiwan.)

Although Hong Kong, Macao, and Taiwan share similar Chinese culture and ideologies with mainland China, due to the social transformation in modern and contemporary society in these four locations, different social and health care systems are in place. This leads to different levels of knowledge and acceptability of HPV vaccines, and accordingly compromises the reliability of pan-China comparison. An organized cervical screening programme has been implemented in Hong Kong, and the coverage was over 40% in 2008 [133]. The Hong Kong government is considering bearing some of the cost of the vaccine in the near future [133]. However, cervical screening is still opportunistic in mainland China, and the HPV vaccine has not yet been licensed. The gap between the places increases the difficulty and complexity of comparison in terms of knowledge of and attitude towards HPV vaccines.

Furthermore, studies in Hong Kong and Taiwan usually publish in English through international peer-reviewed journals or conferences. If they were to publish in Chinese, it would be traditional written Chinese which Chinese databases (like CNKI and Wanfang) would not include. Mainland China uses Simplified written Chinese (Mandarin and Cantonese are the categories of oral Chinese; Traditional and Simplified Chinese are the categories of written Chinese). The two types of written Chinese share the same grammar and sentence structure, but the characters are so different that I am not able to read them.

Study population (but not restricted to)

- Students (high school and college students of all the grades)
- Parents
- Patients
- Health professionals (including physicians, nurses, other)

Instruments (not restricted to):

- Questionnaire survey
- Interview survey
- Interview-administrated questionnaire survey

Sampling methods (not restricted to):

- Cluster sampling
- Random sampling
- Convenience sampling

Examples of outcomes may include

- Knowledge of HPV infection and vaccination, such as symptoms, transmission of HPV infection, and risk factors of cervical cancer;
- Attitude towards HPV, cervical screening, and HPV vaccination;
- Factors affecting people's intentions to be vaccinated, such as knowledge regarding cervical cancer and STIs, perceived risk and severity of cervical cancer, and perceived barriers to vaccination.

No limitations were applied to study size.

Exclusion criteria

Exclusion criteria were:

- Studies that were not based on the original data, such as opinion pieces and general reviews (non-systematic reviews);
- Studies in which the knowledge and attitudes of respondents were not discussed in the result;
- Sample populations not selected in mainland China.

Selection procedure

The selection process had three stages. First, I reviewed the titles and authors of studies on the CNKI and Wanfang databases. The three types of papers are located across four databases: three are CNKI sub-databases categorized by peer-reviewed journal articles, conference articles, and doctoral/master's dissertation theses, and one is the Wanfang database. Second, I pooled the included studies from each database together to exclude duplicates. Third, I screened studies by titles and abstracts and followed the steps of the PRISMA flow chart [134] to screen studies for inclusion. Finally, I read the full text of screened papers and decided which would be included in my systematic review.

2.3.3 Quality assessment

Quality assessment is viewed as a critical part of the systematic review process before data synthesis takes place, and can help the reviewer to evaluate the strength of the evidence [134]. It assesses the risk of bias of individual studies in terms of method and outcome level, indicating the influence of bias and the study in the synthesis [134]. Moreover, it assesses bias across studies as well, suggesting the potential publication bias, for example, in the report of the synthesis of results [135]. Hence, for this step I sought to find an appropriate tool to undertake a quality assessment of the selected papers.

A number of challenges have to be addressed in planning for quality assessment of the Chinese literature. There are no standard guideline for conducting studies and reporting findings in China. There are a large number of quality assessment tools available in the Western literature, but are many designed for clinical trials carried out in a specific setting. My systematic review includes surveys carried out in diverse settings across China. No quality assessment tools have been specifically designed for studies carried out in China and compared to using quality assessment tools in the Western literature for Western research methodology. In choosing a quality assessment tool to use in my systematic review I had to compare existing tools in the Western literature and chose one that may be most appropriate for my review, recognising the need to find a tool that could accommodate the cultural setting in which the primary research was carried out. Details are presented below.

Quality assessment tools for use in systematic review of observational studies

Many quality assessment tools (of the number of checklists and scales is over a hundred) have been reported in the literature [136-141]. But no agreed "gold standard" quality assessment tool exists currently for widespread use. For my systematic review, I chose the tool based on the need to include key characteristics. Some reviews [136, 138] focusing on quality assessment tools provided the evidence needed to guide my choice (see the flow diagram in Figure 2-1 of the selection procedure for quality assessment tools).

Sanderson 2007 [136] reviewed 86 tools for observational studies and provided recommendations for assessing their quality: "The tool should 1) include key domains; 2) be as specific as possible in terms of study design and topic, for example whether it is about economic impact, health outcomes, or patient reported outcomes, whether it is a prospective study (e.g. cohort study), a retrospective study (e.g. case-control study), a cross-sectional study (the type mostly found in my review), or randomised control trials; 3) be a simple checklist rather than a scale; 4) show evidence of development, of validity and reliability". The key domains include: methods for selecting study participants; measurement of variables; other bias; confounding control; and statistical methods [136, 138]. Moreover, the purpose of the assessment tool purpose needs to be considered as well [136], for example, whether it was intended for single use in a specific systematic review (e.g. cost effectiveness or clinical trial), or was a generic tool for systematic reviews (e.g. for all the cross-sectional studies), or was only for use in critical appraisal.

Deek's review, recommended by York University Systematic Review Handbook, identified nearly 200 tools used for the non-randomised studies [138]. Fourteen of them were viewed as the "best tools", as they covered at least five out of six internal validity domains and three out of four core items—the indicators that are used to assess the quality of the tool. Of these 14, six were recommended as being suitable for use in the systematic review of non-randomised studies.

I listed the recommended quality assessment checklists and scales based on these two reviews. Below are the names of the reports featuring quality assessment tools:

- EPHPP, "Quality assessment tool for quantitative studies" [139];
- Newcastle-Ottawa quality assessment scale (for case-control and cohort studies)[140];
- Downs, "Feasibility of creating a checklist for both of the randomised and non-randomised studies of health care intervention" [137];
- Zaza's "Data collection instrument and procedure for systematic reviews in the 'Guide to Community Preventive Services'"[141] ;
- Cowley, "Prostheses for primary total hip replacement. A critical appraisal of the literature" [142]
- SIGN (Scottish Intercollegiate Guidelines Network)'s handbook [143]

Figure 2-1 presents the flow diagram for the selection of quality assessment tools.

The inclusion/exclusion of quality assessment tools for my systematic review

In consideration of the tool's key domain, purpose, ease of use, and development, I chose Zaza's checklist as the quality assessment tool for my review. The comparisons of the characteristics of the 7 tools are listed in Table 2-2.

<u>Exclusions</u>

- Topic-specific use of reviews: Cowley's checklist [142] and Reisch's checklist [144] are for use in the systematic review of therapeutic studies and other topics. Reisch's checklist is considered to be difficult to use.
- Development not described: Cowley's checklist [142], EPHPP [139], Newcastle-Ottawa [140], and Reisch's checklist [144] showed a lack of evidence of the tool's development.

- Unclear tool purpose: SIGN [143] can be used in a lot of situations and its ambiguous and all-purpose features made it difficult to use for my chosen purpose.
- Use of critical appraisal: my aim was to choose a tool to critically appraise the studies included in my review. The tools [137, 139, 144] that are used only for critical appraisal would not take the context of the systematic review into consideration. They could have been used for my review, as this feature was not among the most significant criteria for exclusion, but would not have been the most appropriate ones.

Inclusion

Down's checklist [137] and Zaza's checklist [141] were included. I chose Zaza's checklist for the following reasons.

- It covered the key domains, including methods for selecting study participants, the measurement of variables; confounding control, statistical methods, and other sources of bias.
- To avoid subjective answers to questions about quality, clear rules and specific examples of answers were provided for a range of circumstances.
- The forms could be adjusted to suit different study designs (experimental studies and observational studies). I was able to choose the one most suitable for my studies.
- It described how it developed, which involved independent assessment by several evaluators.
- It was easy to use and had clear descriptions of how to score items.

Zaza's checklist

Zaza's quality assessment checklist was first reported in the paper "Data collection instrument and procedure for systematic reviews in the Guide to Community Preventive Services"[141], which described the development of the tool, including data collection and instrument evaluation. In terms of the content, six categories (descriptions, sampling, measurement, analysis, interpretation of results, and other) with 23 questions were formulated [141].

Zaza's checklist has been cited by approximately 50 systematic reviews (sometimes together with meta-anlaysis) in last decade (2002–2014). Due to the large amount of work involved, I checked the 50 systematic reviews by abstract instead of full text. Four of the reviews mentioned in the abstract that Zaza's checklist was used for the quality assessment of the study, three of which were reviews of interventional studies [145-147]; one was a review of an observational study [148].

Modifications of Zaza's checklist

I performed quality assessments of the included studies according to Zaza's checklist [141], with modifications for my systematic review. Zaza's checklist was created for general use, and not specific to any study design. My quality assessment tool was made up of five components: description, sampling, measurement, data analysis, and interpretation of results. The tool is shown in Table 2-3.

The modifications to Zaza's checklist were as listed below:

- One component was excluded: one of the six components of Zaza's checklist was excluded in my quality assessment tool, which was "Others". This category was intended for researchers who wanted to add something else based on the specific circumstances of their study. In the "Others" component of Zaza's checklist, no specific items were described.
- Eleven items remained the same: 11 items (items 1, 2, 4, 5, 7–10, and 15–17 of my checklist) out of 23 Zaza's items were cited in my quality assessment tool in the same form as they originally were.
- Five items were adapted: 5 items (items 3, 6, 11, 12, 14 of my checklist) out of 23 of Zaza's items were generated based on the instruction of Zaza's checklist, but their wording was adapted in my quality assessment tool.
- One item was added: item 13 in my checklist (was the power calculation provided) was added.
- Six items were excluded: Based on the study design—a cross-sectional study—items of Zaza's checklist that were related only to intervention or cohort studies were excluded from my checklist.

Scoring of Zaza's checklist for my systematic review

I gave each item in the checklist a score. As items were weighted differently in terms of the importance of the quality in question, I gave them different scores. The rating for the items on the checklist is provided in Table 2-4. Description, sampling, and interpretation of results were given higher scores (a score of 2 for each item), and data analysis and measurement were given lower scores (a score of 1 for each item). The total score was 23.

Based on the scores generated by the tool, included studies were classified into three categories (good, fair, and poor). Below are the boundaries for the different quality levels of the studies.

- Good: A score of 18–23;
- Fair: A score of 14–17;
- Poor: A score of 8–13.

2.3.4 Data extraction

I extracted data in terms of variables and the relationship between variables identified in the individual studies. These variables were based on the outcomes of the studies. The common numerical variables I extracted were the reported levels of knowledge and the attitudes towards and acceptability of the vaccine. The results of the relationship between variables were extracted as text.

I set up a data extraction form to summarize the characteristics of the included studies. These included study date the study was carried out, study setting, participant characteristics, and measurements of knowledge, attitudes, and acceptability. The data extraction form also summarised the main results of each study, including participants' awareness of HPV and the HPV vaccine, knowledge of HPV and cervical screening, and intention to be vaccinated (or to vaccinate their child). Where reported, the predictors of acceptability and attitude were included as well. The data extraction form is provided in Appendix 1.

2.3.5 Data Synthesis

I used a narrative synthesis approach to synthesise the data for my systematic review. The studies included in my systematic review were quantitative ones, but the following factors made it difficult to undertake specific quantitative synthesis such as meta-analysis—pooling the findings of multiple studies in a statistical way.

- The heterogeneous findings reported in the individual studies (some focused on knowledge, others on attitudes)
- The inconsistent questions and indicators used to assess the knowledge and attitudes
- The population variation of study participants (see below for description of included populations)
- The limited number of validated questionnaires

Based on these conditions, the approach I took to data synthesis was narrative synthesis-summarising and explaining findings by using words, text, and tabulation. The techniques I chose to use for my synthesis are listed below. They include textual description, groupings, tabulation, common statistic, graphics, plots, sub-group analysis, and a critical discussion. The common statistic I chose to use was the median, given that the distribution of my findings (such as the percentage of knowledge level) was not symmetrical and that there were outliers (described later in this chapter). The median was thus preferred to present the average percentage, due to the heterogeneity of the studies and findings.

In the preliminary synthesis, I grouped the studies into sub-groups in terms of study location, the rurality of participants, age group, ethnic group, and health professionals. In the exploration of relationships between the groups, I analysed the data based on these groups and then synthesised the results to see whether there was a pattern within or across them. Then, I used exploratory data analysis (EDA), which is a way to assess the population distribution of the variables. I used multivariate graphical EDA—a boxplot, barchart, and a map of China—to present the findings. In the assessment of synthesis, I decided to discuss the limitations at the individual study level and at review level. Limitations may include the selection bias, publication bias, and single reviewer bias.

R statistical programming 3.0.1 (free online) was used to produce the boxplot and barchart. The map of China was generated online (http://www.dituhui.com/favorites/data).

2.4 Results

2.4.1 Study selection

The database searches were run in December 2012. Studies were first reviewed by title and author(s) in each database, and duplicates were excluded. The search identified 251 articles at this stage and their abstracts were then reviewed. I excluded studies whose topic was not relevant to HPV infection and HPV vaccination or to knowledge of and attitudes towards HPV, whose methodology was not a survey, and which were not research reports. Fifty full-text articles were included, and 3 were excluded because of difficulties in data extraction (their results were not clearly presented). Therefore, a total of 47 articles met the inclusion criteria and were therefore included in the systematic review. The selection process for studies is summarised in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram [134], see Figure 2-2. The excluded studies and the reasons for each exclusion are listed in Appendix 2.

2.4.2 Study characteristics

The included studies have been listed by study period, location, setting, instrument, sampling, and characteristics of participants in Table 2-5.

Study period, location, and setting

The study period was 2006–2011, with the majority (65.8%) of the studies being conducted in 2008 (19.1%), 2009 (17.0%), and 2010 (29.8%). The regions included in the studies covered 17 provinces out of 31 provincial regions (22 provinces, 4 municipalities, and 5 autonomous regions) in China, from the west, the north, and the south. The definition of West, North and South China comes from *China Statistical Yearbook* [149], which provides information for central government reporting in China.

Study settings (overlap exists in the categories below, Table 2-5 presents the details)

- Hospital-based setting: 27 studies (57.4%)
- Community-based setting: 9 studies (19.1%)
- College/high school-based setting: 5 studies (18.5%)
- Rural region setting (village-based): 9 studies (19.1%)
- Urban region setting: 22 studies (46.8%)
- Unknown/ not described: 5 studies (18.5%), 4 of which were in West China [150-152]

Study sample size and participants

All of the included studies were quantitative, cross-sectional studies, with sample sizes ranging from 100 to 9,865. Over half of the studies (55.3%) had a sample size greater than 500; one third of studies had a sample size of 1,000 or more.

Study participants

- Gender: Most participants were female, and 5 studies (18.5%) [153-157] included male participants; but only two studies[153, 154] assessed the knowledge and attitudes of both genders.
- Age: Seven (14.9%) included teenagers (13-18 year old) and young adults (18-26 year old) aged between 14 and 26 years old, and 4 of them [153-156] reported the awareness and knowledge in this group separately.

- Ethnicity: Five studies (18.5%) [150, 157-160] examined knowledge and attitudes among minority populations: 4 among the Xinjiang Uyghur people [157-160], 1 among Tibetan women [151], and 1 among Hui women[150].
- Cervical cancer patients: two studies carried [160] out in Xinjiang recruited cervical cancer patients as their study participants.
- Health professionals: Three studies [161-163] explored the issues among health professionals including doctors and nurses.

Study instrument

- Interview: one study used telephone interviews [164]
- Questionnaire surveys: Eleven studies (23.4%) used interview-administrated questionnaires conducted by trained researchers (Table 2-5); the majority (31) of the remaining studies employed self-administrated questionnaires with closed questions. Of these studies, 4 were completed by health professionals (i.e. gynaecologists) on behalf of the participants [158-160, 165]; 3 were completed by health professionals giving their own knowledge and attitudes [161-163]; the others were filled in by the non-professional participants (women, young adults, and teenagers).

Wording of the questions

Different wording of the same question was used in the instruments of the studies in my review. Details are provided in Table 2-6. A summary is presented below.

Thirty-one (66.0%) studies examined the awareness of HPV infection and the wording was different:

- Have you had heard of HPV infection?
- Do you know what HPV is?

Thirty-six (76.6%) studies explored the knowledge of cervical cancer, and the wording again varied:

- Is HPV the main cause of cervical cancer?
- Can HPV lead to cervical cancer?
- Is HPV an essential element in cervical cancer?
- Is HPV related to cervical cancer?
- When HPV is mentioned, what is your first thought?

Sixteen studies (34%) reported on knowledge of STIs, and the wording was the same:

- Is HPV sexually transmitted?

Study sampling methods

Over half of the included studies used probability sampling methods, and fewer than half did not describe their methods. Details are provided in Table 2-5. A summary is presented below.

- Twenty-six studies (55.3%) used cluster or random sampling methods
- One study employed a convenience sampling method
- Others did not describe the sampling method used

2.4.3 Study quality

Overview of the studies' quality

The quality assessment checklist included 17 items in total and except for 4 items (multiple comparisons, multivariate techniques, reliable measurement, and potential bias), the remaining items in the checklist were met by approximately 50% of the studies. Details are presented below and are also provided in Figure 2-3.

- Eight of the criteria were met by 38 (approximately 80%) of the studies. These criteria included: description of the study population, outcomes, statistical tests, and study instruments.
- Five criteria were met by 23 (approximately 50%) of the studies. These criteria included: inclusion/exclusion criteria for the study population, the assessment of confounding, at least 80% of enrolled participants completing the study.
- Four criteria were met by 5 (10.6%) of the studies. These criteria included: multiple comparisons, detailed descriptions of the instrument's development, and descriptions of potential bias.

Based on the scores given to each paper, the included studies were categorized into good, fair, and poor quality. Eleven studies were ranked as good quality studies (having scored 18–22) [98, 131, 132, 165-172], the majority of my included studies, 25 in total, were ranked as fair quality studies (having scored 14–17), and the remaining 11 studies were ranked as poor quality (having scored 8–13) [152, 155, 157, 159, 164, 173-178]. Details of the distribution of the different quality studies (with scores) are provided in Tables 2-7 and 2-8, and Figure 2-4. The table in Appendix 3 presents details of the quality of each included paper.

Characteristics of good quality studies

Good quality studies were good at sampling, measurement, data analysis, and the interpretation of results:

- Description: The study population was well described in terms of its demographics.
- Sampling: The sampling frame was specifically provided in terms of the date, location, participants, and study instrument.
- Measurement: The measurement was mostly valid and had clearly defined outcomes.
- Data analysis: The statistical methods were described, and the power calculation provided. Confounding was assessed and controllable variables were corrected when necessary.

The most common feature of good quality studies was larger sample sizes. Eight out of 11 good quality studies had over 1,000 participants. The most common weaknesses among good quality studies were a lack of assessment of the measurements' reliability, and of evidence (i.e. theory-based model) of the instrument's development. Hence, it is difficult to identify how these studies generated the questions and the extent to which participants' responses reflected their real knowledge and attitudes.

Furthermore, geographical patterns were found in the quality of the studies (See Table 2-9 and Figures 2-5, 2-6 and 2-7). No studies carried out in West China (Xinjiang, Sichuan, Yunnan and Qinghai) (12 studies) were of good quality, and 5 (41.7%) were of poor quality. Studies carried out in North China were mostly of good quality, with one exception [177]. Descriptions of the poor studies are presented below.

Moreover, there was no clear pattern in terms of the settings of the studies, given the lack of evidence of studies. None of the college/school-based studies were of good quality. There was no relation between date of publication (2008–2012) and whether or not a study was rated as good quality.

Characteristics of fair quality studies

The methodological strengths and weaknesses of the studies rated as 'fair quality' varied considerably. Some of them described a specific sampling frame, assessed the confounding, and made stratifications on the basis of demographics to adjust controllable variables. However, some did not provide inclusion/exclusion criteria for study groups, mention what percentage of the enrolled participants complete the study, or have a reliable measurement method.

There was no evident association of fair quality studies with sample size, geographical locations, study setting, or date of publication.

Characteristics of poor quality studies

The 11 studies rated as 'poor quality' studies shared some common weaknesses. Details are presented in the Table 2-7 and in the table in Appendix 3

- Sampling methods were not described in the poor quality studies, including:
  - How they collected the sample (Was it a random or a convenient sampling?)
  - How the participants were recruited
  - What the representativeness of the population was

- The instrument (questionnaire) was not evidence-based**.** Most studies reported the questions included in the questionnaire in a table, but the following issues regarding instrument development were not clear:
  - What the questions were based on
  - Whether there was a theoretical model for the development of the questionnaire
  - Whether there was a pilot study or cognitive interview to validate the instrument

- No controllable variables were corrected or bias was limited**.** The 11 poor quality studies did not conduct any stratification or statistical adjustment to correct controllable variables (such as age, gender, and education). Even in the data-collection process, measures for confounding control had not been considered. Study results were mostly presented by descriptive analysis rather than association analysis.

There is some evidence of a geographical pattern in the poor quality studies. Half of the poor quality studies were from West China—four from Xinjiang [152, 157, 159, 176] and one from Sichuan [174].

Small sample size may be a factor in the poor quality studies. The typical sample size of the poor quality studies was 100–500, with the exception of one study, which recruited approximately 800 participants. Compared with sample size of the fair and good quality studies—1,000 to 9000—the smaller sample size may imply limited research resources and poor quality fieldwork.

2.4.4 Results of individual studies

The main results of the individual studies are summarised in Tables 2-5 and 2-6. Awareness and knowledge of HPV and cervical cancer, and of the sexually transmitted nature of the HPV infection, and information on the acceptability of HPV vaccines are listed, as well as a comparison of study quality and the wording of questions. Additional findings (e.g. knowledge of HPV and genital warts, influencing factors in acceptability of the HPV vaccine) from included studies are detailed in Appendix 1.

Of the 47 studies included in my review, a few of them need to be highlighted.

M. He's study in 2011 [169] is the only cross-regional (seven regions of China) study in my review with a relatively robust methodology (rated as a good quality study) and had the biggest sample size (9,865 adult women and 780 health professionals). Although no geographical pattern of knowledge and attitudes was reported in this study, this particular feature was not actually examined and the study's findings were not displayed based on different locations. Hence, He's study was not included in the later synthesis because of its cross-regional participants. The recruitment of participants in urban hospitals of tier-one cities suggested the findings (participants had a moderate level of knowledge, and a high level of acceptability) be more generalised to wealthy and well-educated people. Population migration may compromise the conclusion, although this information was not explored in the study.

A. Guzhalinuer's study [159] in 2007, together with A. Gulinuer's study [160] in 2009, were the earliest papers (both surveys were carried out in 2006) included in my review, and did not explore the acceptability of HPV vaccines. These two studies were also the only ones in which the questionnaires were filled in by the gynaecologists on behalf of participants. The lowest knowledge (0%) of HPV infection was found in Guzhalinuer's study of Uyghur cervical cancer patients in urban hospitals in Xinjiang. The poor quality and early date of this study may compromise the findings. C.L. Ren's study [150] in 2010 was the only one to compare differences between ethnic groups in the level of knowledge of HPV causing cervical cancer: in this study Uyghur women had the lowest level of knowledge (5.2%), then

Hui (11.5%), then the Han population (20.6%). The lack of information on the study setting and details of recruitment limit the generalisability of results.

L.N. Xu's study [166] from 2009 and B. Cui's studies [131] in 2010 and in 2008 were good quality studies which recruited participants from a wide age range (15–59 years in the first two, 15–54 years in the latter): teenagers, young adults, and adults. Their methodology was of a good quality, and differences were found between urban and rural areas in the former two studies. Nevertheless, no findings were reported in terms of specific age groups in these studies. A further five fair quality studies had the same feature, they are: D. Song's study[179] in 2007 (15–54), J. Li's study [167] in 2008, D.J. Zhao's study[180] in 2010 (16–54), L.X. Zhou's study[181] in 2011 (16–55), and Y. Zhou's study[177] in 2011 (17–59).

2.4.5 Synthesis of results

Awareness of HPV and knowledge of the relationship between HPV and cervical cancer, and of the sexually transmitted nature of HPV were the main issues examined in the studies included in my review. Figures 2-8 and 2-9 show the number of studies that explored individual items relating to knowledge, awareness, and the acceptability of the HPV vaccine. Outliers of data estimates existed in poor quality studies (Figure 2-10). Hence, the results from poor quality studies were less reliable when they were synthesised together with other included studies, and they were excluded accordingly when the median level of awareness and knowledge was calculated. The data presented below relates to the median estimate of the percentage and range of awareness and knowledge of HPV and the HPV vaccine. Studies of all levels of quality are shown in Table 2-9. The findings of the data synthesis are presented below.

The overview of awareness and knowledge of HPV

Thirty-two good and fair quality studies and 7 poor quality studies included in my review reported on awareness, and two examined mainly knowledge (see above) among different groups of people in West, North, and South China. Figures 2-10 and 2-11 show the overview of awareness and knowledge in terms of differences in rurality, region, and study quality in boxplot of synthesis of results.

The overall awareness was 31% (11–46%) for urban adult women and 9% (6–27%) for rural adult women. Awareness varied across different population sub-groups, Uyghur women had the lowest awareness (3.5%; 0–7%), followed by teenagers (10%, no range available as only one study undertaken among teenagers), and young adults (29%, 17–50%), and the health professionals had the highest awareness at 90.5% (85–92%). See Tables 2-10 and 2-11.

The knowledge of HPV among the participants in the included studies showed a similar pattern to awareness levels. The two most commonly identified knowledge items are listed in Tables 2-10 and 2-11 (knowledge of relationship between HPV and cervical cancer, and knowledge of the sexually transmitted nature of HPV). Other knowledge items were also examined. For example, 'Do you know that HPV is asymptomatic? 'or 'Do you know that having multiple sexual partners could increase the risk of getting HPV infection?', but the low number of studies (< 8) with a diverse study population limited the possibility for further data synthesis. Hence, these findings are summarised later in this chapter in text form. Figures 2-12 and 2-13 compare the two main knowledge criteria in different groups of people. 31% (9–57%) of urban adult women were aware of the relationship between HPV and cervical cancer; the percentage was 6% (3–49%) for rural adults, 7% (0–14%) for adult Uyghur women. , 19% for teenagers (no range available as only one study undertaken among teenagers), 55% (53–75%) for young adults, and 79% (66–84%) for health professionals. 36% (20–55%) among urban adult women were aware of the sexually transmitted nature of HPV, 19.5% (1–38%) for rural adults, 0% for adult Uyghur women, 16% for teenagers (no range available as only one study undertaken among teenagers), 60% (46–76%) for young adults, and 85% (78-92%) for health professionals.

Differences by demographic of participants

As a wide range of groups of participants were included in the systematic review, in order to report the results with less confounding, comparison was made between similar categories in terms of demographies. Seven poor quality studies were excluded from the estimate of median and comparison (see Tables 2-10 and 2-11).

Differences by location and rurality

Twenty-four good and fair quality and five poor quality studies reported differences of awareness and knowledge of HPV and cervical cancer according to rurality. The awareness and knowledge varied according to the regions from which the sample was collected. People from South China tended to be more aware and knowledgeable about HPV than those from North and West China, while people from West China had the lowest awareness. This geographical trend was observed among urban and rural adults (participants excluded teenagers, young adults, health professionals, and minority ethnic groups). Rural adults showed less awareness of HPV than those from urban areas.

Figure 2-12 shows clearly the pattern among urban and rural adults in different parts of China, in terms of the awareness and knowledge. From West, North, and South, the awareness was 23.5% (11–45%), 27.5% (12–46%), and 37.5% (21–41%) for urban adults, and 9% (6–17%) and 15.5% (4–27%) for north and south rural adults (no data was reported from West China). The knowledge of HPV and cervical cancer and the sexually transmitted nature of HPV are also presented in the figure.

Differences by ethnicity

Two fair [158, 160] and one poor quality [159] study reported levels of knowledge among Uyghur people. Two of them recruited cervical cancer patients as their participants [159]; these were the only two studies of my review that were carried out among cervical cancer patients. Of the Uyghur respondents, 3.5% (0–7%) had heard of HPV [158, 160]; this figure was lower than in all the other studies. The knowledge of the link between HPV and cervical cancer and of the sexually transmitted nature of HPV were low, at 7% (0–14%) and 0% [158, 160]. Figure 2-13 presents these results graphically in Uyghur people compared to other population sub-groups.

Differences by age

Three fair [153, 154, 156] and one poor quality[155] study were carried out among teenagers and young adults—school/college-age students. Teenagers [156] had the lowest awareness (10%) and knowledge (19% knew of cervical cancer, 16% knew about its sexually transmitted nature); this was generally the same as for rural adults in North China, but lower than rural adults in South China.

Young adults had relatively high awareness (21%; range of 17–50%) and knowledge (55% with a range of 53–75% for the link between HPV and cervical cancer; 60% with a range of 46–76% for the sexually transmitted nature of HPV)[153, 154]. The level of knowledge was even higher than that of urban adults. Figure 2-13 presents these results graphically in teenagers and young adults in contrast to other population sub-groups.

Differences by gender

Two fair quality studies [153, 154] conducted in colleges reported the influence of gender on knowledge. They indicated that male students know more (35.5%, range: 21–37%) about HPV than female students (27%, range: 17–37%) [153, 154]. However, the significance of these results is unclear due to the limited available evidence.

Knowledge and awareness among health professionals

Three fair quality studies [161-163] reported that health professionals (referring to obstetricians, gynaecologists, and nurses) had the highest awareness (89%; range: 85–92%) and knowledge (79% with a range of 66–84%; and 85% with a range of 78–92%). Figure 2-13 presents these results graphically in health professionals in contrast to other population sub-groups.

Other findings: misconceptions about the HPV infection and vaccine

The asymptomatic nature and self-clearing nature of HPV infection

One fair quality and two poor quality studies explored knowledge about HPV infection. Few participants knew that HPV infection could disappear spontaneously or be asymptomatic. Among obstetricians and gynaecologists, 34.3% knew that HPV infection could be self-clearing [163], compared to 17.1% among adult women [177]. In terms of the asymptomatic nature of HPV, 15.6% of adult women [177] and 62.2% of college students [155] knew this fact.

Risk factor of HPV: having multi-sexual partners

One good quality [168] and two fair quality studies [153, 156] explored the increased risk of being infected with HPV by having multiple sexual partners, but they focused on different populations. These studies suggested that more male college students (76.2%) answered correctly than females (71.7%), but the result was not statistically significant [153]; 63% of teenagers[156] and 90% of urban women adults reported knowing about this risk factor [168].

The general acceptability of the HPV vaccine

Twelve good and fair quality studies and one poor quality study included in my review explored respondents' willingness to be vaccinated, and 8 of them examined the willingness related to the participants' daughters (See Figure 2-14 and Table 2-12). For adult women, the acceptability of the HPV vaccination both for themselves and for their daughters were generally the same in North China (76.5% and 75%), and both figures were lower in South China (48% and 59%). Health professionals in North China tended to have lower acceptability for their daughters (28%), although the acceptability for themselves is higher (74%). No data was reported in West and South China for health professionals. These results are presented in Table 2-12.

Eight studies explored the influencing factors in the acceptability of HPV vaccination, and Table 2-13 presents the results of these studies. The appropriate age, cost of the vaccine, and the source through which the vaccine was offered were presented in a descriptive way in these individual studies in my review; concerns about the vaccine's adverse effects, effectiveness, and changes to future sexual behaviour are examined in the multivariate analysis of the individual studies. Details are shown below.

The acceptable cost that people would be willing to pay

Two good [167, 169] and 6 fair quality [163, 179, 180, 182-184] studies examined the cost issues related to the HPV vaccine. A total of 55.2% (41.5–67.2%) of the participants wished the government could cover the whole cost of the vaccine. W. Xiao's study and D.J. Zhao's study reported that 84.2% and 93.9% of the participants would be willing to pay up to ¥100 ($16) for the vaccine. Y. Wu's study found 71.2% of respondents indicated they wished to pay less than ¥500 ($80) for the vaccine.

Acceptable sources for vaccine in the future

Two good [167, 169] and 5 fair quality [179, 180, 182-184] studies examined participants' preferred source for the HPV vaccine in the future. Overall, 56.2% (55.4–82%) of the respondents would prefer to receive the vaccine if it was offered by the government, and 35.7% would prefer to receive vaccines offered by medical institutions.

The appropriate age for vaccination

Three good and fair quality studies and one poor quality study explored the vaccination age. The fair quality study found that 72.4% of the health professionals believed the appropriate age for vaccination to be over 18 years old for girls [163]. The same results were also found among adults in two other good quality [167, 169] and one poor quality study [177]. M. He's study [169] found that 10.7% of health professionals believed that married people should be the vaccination group, the other two studies did not provide specific proportions [167, 177].

Factors affecting willingness to accept HPV vaccine

Two good [167, 169] and four-fair quality [163, 180, 183, 184] studies examined the potential factors that might inhibit participants' acceptance of HPV vaccines. These studies all explored the following two issues with a closed question using the same wording. Details are shown in Table 2-13.

- No perceived risk of cervical cancer: 37.2% (4.9–68.6%) of respondents did not perceive they were at risk of cervical cancer.
- Concerns about vaccines not being used on a large scale: 43.6% (12.3–63.9%) of respondents worried that the vaccines were not being used on a large scale.

The other factors included:

- Concerns about vaccine's adverse effects: How many people worried about the safety of the vaccine in the studies in my review?
    - 61.8% of adult women and 69.0% of health professionals [169]
    - 67.3% of health professionals [163]
    - 26.6% adult women [183]
    - 24.1% of adult women [167]
- Concerns about the vaccine's effectiveness: How many people believe HPV vaccines could effectively protect humans from cervical cancer in these studies or hope it to be 100% effective? ('Hope the HPV will be 100% effective' is one of the options respondents can choose in the questionnaire used in these studies.)
    - 54.8% of health professionals [163]
    - 19.2% of adult women [183]
    - 63.3% of urban adults hoped the HPV vaccines would be 100% effective [180]
    - 65.9% of women adults believed the vaccine would be 100% effective[167]
- Concerns about changes of future sexual behaviours: How many people were concerned that HPV vaccines would increase high-risk sexual activity?
    - 54.1% of the health professionals were concerned about this [163]

No further stigmatising attitude towards HPV infection was explored in the studies included in my review.

2.5 Discussion

2.5.1 Key findings and interpretation

My systematic review is the first I am aware of to examine and synthesise the awareness and knowledge of HPV in different geographical areas of China (West, North, and South China), and also the first to make comparisons among different groups of Chinese people—Uyghur compared to the rest of the population (teenagers and adults), teenagers compared to young adults, urban compared to rural adults, and adult women compared to health professionals. Based on my review, differences of location and diversity in demographics might account for the different level of awareness, knowledge, and acceptability of HPV and vaccination.

Awareness, knowledge, and acceptability

In general, the awareness of HPV varied across different regions of China and groups of people in my review. The main contributors to the significant differences were location (West, North, and South), rurality, ethnicity, age, and whether or not the participants were health professionals. But rurality and ethnicity might be partially explained by the lower socioeconomic status of those groups. Uyghur and rural people live mostly in deprived regions with lower socioeconomic status and limited health resources. Details of the interpretation are discussed later in this section.

The most frequently examined knowledge items were the relationship between HPV and cervical cancer, and the sexually transmitted nature of HPV. One weakness which might undermine the level of knowledge in the studies in my review was the difficulty in discriminating between participants in the studies who were already aware of HPV, and those who were not just prior to answering the knowledge questions. If the participants did not know about HPV, their knowledge of the relationship between HPV and cervical cancer and the sexually transmitted nature of HPV would not be accurate. But another possibility was that people would be more aware of HPV when it is related to cervical cancer and sexually transmitted disease rather than when they were asked about HPV alone. Hence, the results may have underestimated or overestimated the level of knowledge among participants.

In general, the acceptability of HPV vaccines varied in terms of the vaccines' target recipients (for oneself or for one's daughter) and the participants' health knowledge background (i.e. whether from the general population, or a health professional). The cost, source, and appropriate age for the HPV vaccines were the most examined issues in the studies.

The impact of the demographic of participants on knowledge and attitudes

Findings for some specific populations highlight the need to implement tailored HPV vaccination information campaigns. The first group of people that needs to be emphasised is the Uyghur population, who had very limited knowledge of HPV. The second is health professionals, who displayed a lack of specialised knowledge regarding the HPV vaccine. The third group is female students in schools and colleges, who had a lower level of knowledge than males. Details are presented below.

Ethnicity: Uyghur people

The Uyghur population had the least awareness and knowledge compared to the majority Han population in China. A number of factors likely contribute to this. The Uyghur population resides in West China—a remote and less developed area. They have a completely different culture (most of them are Muslim) from the majority Chinese population, live in low economic conditions, receive a low level of education, and speak Uyghur and low levels of Mandarin; however, Mandarin is the language used for health education. These cultural and socioeconomic factors might contribute to the low levels of health-related knowledge among the Uyghur population.

Moreover, three Uyghur studies were conducted through convenience sampling. Hence, limited sampling methods might be responsible for the less reliable results and thus limit their generalisability to the wider Uyghur population. Further, acceptability of the HPV vaccine was not examined in four Uyghur studies, and the predictive factors were not known, but there is some evidence [185, 186] that ethnicity is an important factor affecting the acceptability of HPV vaccination in the UK, where Muslim individuals were less likely to accept the vaccination. The extent to which specific religious or cultural beliefs may affect the acceptability of the HPV vaccine in Uyghur Muslim populations is unknown.

Health professionals

The health professionals lacked some specialised knowledge of HPV infection and vaccines (e.g. the type-specific outcomes of HPV, the optimal age for vaccination, and the purpose of screening) [187]. The reported low levels of acceptability of the HPV vaccine for their daughters (28%) may reflect the uncertainty of health professionals about the vaccine's effects and safety. This lack of knowledge and uncertainty about the vaccine among health professionals might affect the advice they give to patients and the public. However, it is important to note that this low acceptability of health professionals of HPV vaccination for their daughters was only reported in one study (fair quality), carried out in one province with approximately 200 health professionals. Therefore the external validity of this finding is limited, and further studies with health professionals are needed before any firm conclusions can be made.

Age, rurality, gender, and other factors

Teenagers in school, young adults in college, and adult women in rural areas had a similar level of awareness and knowledge, which was lower than that of adult women in urban areas. There is some indication that male students had more knowledge than female students, but confidence in these results is limited because this finding appeared in only two of the studies [153, 154]. Differences in knowledge by age may be attributed to differences in the level of education; rurality differences may be associated with socioeconomic status and limited health care services; and gender difference may be due to the conservative culture in China, where female students might feel embarrassed more often than males when inquiring about sexual issues in public and thus, have less knowledge. Very few studies (<8) in my review explored attitudes and acceptability, and the limited evidence prevented me from finding patterns in age, gender, and rurality.

The findings of my review suggest demographical variations in knowledge about and attitudes towards HPV and vaccination. They also imply the health disparity existing in the diverse groups in China. Participants' demographic characteristics might be associated with access to health care; for example, ethnic minority groups and rural adults may have a low level of socioeconomic status, live in deprived regions, and accordingly have less health care facilities and personnel. Hence, the implementation of a widespread vaccination programme needs to take health inequality into account.

2.5.2 Methodological issues

My systematic review has some methodological strengths and weaknesses in relation to search strategy, study quality, selection bias and instrument development. See below for detailed discussion.

Search strategy

The generalizability of my systematic review may be limited by my search strategy (determined by the objective of my review and feasibility of obtaining papers) – the time period covered, language included and locations covered. My search in the Chinese literature in the two databases (CNKI and Wanfang) finished by December in 2012, so literature published after this date would not have been included. However, my review provides evidence of synthesis of results in the areas of knowledge and attitudes up to 2012, from which time point further updates would be valuable. There are language and location limitations in my search: , the search strategy was limited to studies located Mainland China increase the comparability of results across studies.

I have identified approximately twenty additional publications in the Chinese literature that may match my inclusion criteria in the two databases since 2012. Although not part of my systematic review, my initial scope of these new papers has found that more geographical regions are included, and more areas of attitudes towards HPV vaccination were discussed, than were included in the papers included in my systematic review. As my systematic review reported in this chapter was completed in 2013 I have not included these updated papers in my thesis. However, I plan to review these papers in more detail and will include relevant data in future publications.

Study quality

It is difficult to identify whether the study quality had an influence on differences in awareness and knowledge. For example, it seemed that the difference of study quality had an impact on the reported awareness of HPV. The level of awareness of HPV was 26% (6–39%), 21% (-646%), and 12% (8–45%) respectively for good, fair, and poor quality studies [173, 175, 176]. But when the study location is taken together with the study quality it becomes clear that poor quality studies were mostly performed in West China, and good quality ones were carried out in North and South China. I may thus conclude that the factors that contributed to the difference in awareness were probably rurality or ethnicity.

Selection bias

Selection bias likely exists in the included studies due to the lack of evidence and description of recruitment, sampling methods, and response rate. It is difficult to conclude if the results of the studies can be generalised to the wider population.

Except for two studies which recruited participants from local register agencies, the others did not provide details about the recruitment process, although the study setting was mostly reported. Five studies did not describe the study setting [150-152, 183]. The following questions are unanswered in most studies:

- Was the sample collected by door-to-door interviews or household registration?
- Were the participants contacted by post, telephone, or another means?
- Was there a reminder sent to the participants to improve the response rate?

Out of a total 47 studies, 27 reported they had used convenience, cluster, or random sampling in the selection of participants, but none described the details of the sampling methods, such as:

- How clusters were selected
- How elements were identified in each cluster in the cluster sampling?

Twenty of 47 studies did not report which sampling method they had used.

Half of the studies (24) did not report on the following issues regarding response rate.

- What was the response rate in the survey?
- How many people approached, agreed to attend, and finally completed the survey?

Sample size

A larger sample size may suggest sufficient research resources and networks and the capacity to carry out big fieldwork projects. My review indicates that sample size might be related to study quality and study setting. Approximately 80% of the good quality studies had a sample size greater than 1,000, and all the poor quality studies had a sample size smaller than 500, with one exception, which had a sample size of 800. Twelve out of the 21 population-based studies had a sample size greater than 1,000, most (24/27) of the hospital-based studies had a small sample size (<1000). Bigger samples may be more generalisable to the wider population, but the sampling methods should also be taken into account regarding the representative.

Instrument

<u>Lack of an evidence-based instrument:</u> All the included studies lacked descriptive evidence of the instrument's development. None of the studies used a theory-based model to formulate the questions. Questions generated from Li's study's instrument [124] were commonly used in other studies.

<u>Closed questions with dichotomous choice:</u> Closed questions were employed in all the included studies, with a dichotomous choice response (participants were asked to choose "yes" or "no"). Compared to the 5- or 7-point Likert scale of response, commonly found in

Western literature, a dichotomous option might reflect limited details of the participants' attitude toward HPV infection and vaccines. Open-ended questions were found in the only interview study in my review, but detailed descriptions of participants' responses were not provided.

Wording of the questions: It is difficult to identify whether the wording of the questions had any impact on levels of awareness and knowledge. For example, among Uyghur people, in terms of knowledge of the relationship between HPV and cervical cancer—with the exception of one study, which reported 14% of participants had the relevant knowledge (the same wording of the question was used in another Uyghur study revealing 0% knowledge)—no Uyghur participants answered correctly no matter what the wording of question was [150, 158-160].

Interpretation of results

Brief discussion: The Chinese literature in my review usually had a very short discussion section (which usually reported some methodological limitations and limited comparisons with Western literature). The requirement of a word limit in Chinese academic journals may contribute to this. Furthermore, Chinese studies were less likely to criticise on both themselves and other studies. Comparisons were made between studies (Chinese-Chinese, Chinese-Western), but critique was rarely found in these papers; for example, discussion on bias and confounding were ignored by most of the studies in my review.

Single reviewer

An additional limitation is that all steps in this systematic review of the Chinese language literature is, of course, that it was carried out by only one reviewer. I recognise that normally study selection based on review of abstracts and titles, reading of full text papers, quality assessment and data extraction steps are carried out by at least two reviewers. Given the language barrier inherent in this review, this was not possible. The objective of my systematic review was to review Chinese-language literature. The two databases I searched had English-language versions, but these were at very rudimentary level, not equivalent to the Chinese-language version in terms of the extent of the included Chinese literature, or the structure and layout of the databases. Moreover, there were no researchers including my supervisors in my Centre who were able to read and understand Chinese literature at the time I was doing my systematic review. Hence, it was not possible to have two reviewers reading the papers. However, I discussed each step and the content of included papers in detail with my supervisors at each stage (study selection, data extraction and data synthesis) to reduce the single reviewer bias as much as possible.

2.5.3 Comparisons with previous similar literature

Comparison of findings

Some of my findings were confirmed by a few systematic reviews, published since 2007, regarding knowledge of and attitudes towards HPV and vaccination. They are:

- The low-moderate level of awareness and knowledge of HPV in China, comparable with other Asian and sub-Saharan African countries [188] [189]
- The high level of acceptability of HPV vaccines in China, the same as in sub-Saharan Africa[188] [189]
- The difference of awareness and knowledge among young adults and teenagers, the same as in Europe [190]
- The high level of knowledge among health professionals [68]
- The impact of ethnicity, similar to a review among people in the US [191]
- The most examined (most concerned or not) predictors of HPV vaccines [191] [192]

However, some of my findings were not consistent with the published studies:

- The difference in awareness and knowledge between males and females [68] [190]

The diversity of results described in published systematic reviews may limit reliable direct comparisons. Some further details and interpretation is given below.

A. Young's systematic review [188] was the first to examine HPV awareness, knowledge, and acceptability among Asians, including the Chinese (4 studies), Malaysians (1), South Koreans (1), and Thai populations (1) from 2006 to 2010. Mainland Chinese had the lowest level of awareness (16%), a moderate level of knowledge of HPV and cervical cancer (48%), and the highest level of acceptability of HPV vaccines (85%). The findings were generally similar to those in my review, but the comparison is less reliable as considerable variation (the survey methods, age groups of participants, and measure of awareness, knowledge, and acceptability) was found in the individual studies included in the Asian-Pacific review [188]. Perlman's systematic review, carried out among Sub-Saharan African populations [189] in 2014, had some similar findings to mine, i.e. that Africans from 6 sub-Saharan countries had a high level of HPV vaccine acceptability but low levels of knowledge and awareness of cervical cancer, HPV, and vaccines [189].

Marlow's systematic review of studies among UK ethnic minorities carried out from 2006 to 2009 reported different levels of acceptability of HPV vaccination—Chinese, 40%; other Asians, lower than 25%; and white and black, higher than 50% [185]. These findings suggest that Chinese people have relatively high acceptability among Asians, but still lower than the white and black groups. The sense of identity of Chinese people living abroad might partly explain the relatively low acceptability, even lower than the Chinese living in China.

Samkange-Zeeb's systematic review of studies carried out among European school-going adolescents from 1990 to 2010 [190] assessed awareness and knowledge of sexually transmitted diseases (STDs). Two studies included in the review, by M. Gottvall M [193] and C. Pelucchi [194] in 2008, found that young adults (71.6%) had a higher awareness of HPV than teenagers (16.4%). Males (young adults: 47.4%; teenagers: 5.4%) were less knowledgeable than females (young adults: 64.9%; teenagers: 12.1%) in terms of the sexually transmitted nature of HPV infection. The same gender pattern was also reported in an early systematic review in which studies on people in the US and UK formed the majority [68]. The review also found a high level of knowledge (of the link between HPV and cervical cancer, and of the asymptomatic nature of HPV) among health professionals (nurse practitioners, general practitioners, gynecologists, and physicians), which was 59–100% [68]. My review showed a similar pattern of awareness of HPV in young adults and teenagers, but difference between the two sub-groups was not that huge, and a similar high level of knowledge among health professionals.

Nevertheless, the differing level of knowledge between males and females was found to be opposite in my review, and this might be explained by the lack of robust evidence in my review—there were very few good quality studies. It might also be explained by the social desirability bias. Female students in China would be more inclined to present themselves in a socially acceptable way to gain the approval of others. A conservative attitude towards sexual practices still exists in China, and female Chinese students might think that being knowledgeable on matters relating to sex is not good or acceptable for girls, so they may be more likely to conceal their knowledge when answering the questions in the survey. Male students may have fewer such considerations. But the limited evidence of the studies in my review is not robust enough to draw a firm conclusion.

S. Klug's systematic review, which reported on studies carried out in Western countries (mostly in the US) and published in 2012 [191], explored the predictors of HPV vaccine uptake. Ethnicity, the place of vaccination, and the age at vaccination were found to have impact on both the initiation and completion rates of HPV vaccination. But this study was conservative in describing the impact of ethnicity, considering that it may be related to socioeconomic status and health insurance [191]. My review also found differences among ethnicities (Uyghur) in the knowledge of HPV and vaccines, and explored the potential health inequality that might be caused by the related location, culture, education, and health access. Hence, the impact of ethnicity on knowledge and acceptability of HPV vaccines requires exploration through further studies.

L. Garcini's systematic review [192] of studies among US residents and also published in 2012 found that demographics and access-related issues (health providers' recommendation and insurance coverage) were the most recognised factors influencing acceptability of HPV vaccines from a parental perspective. My review found the most frequently examined factors thought to be associated with HPV vaccine acceptability were the cost, followed by the source through which HPV vaccines were offered, and the vaccination age. However it is important to note that this is not a definitive ranking of the predictors of vaccine uptake among Chinese populations - I am not able to draw any conclusions on the relative importance of these due to the very limited evidence.

To summarise, it is difficult to draw any definite conclusions based on the comparisons between my review among Chinese populations and other reviews carried out among other population groups. As several factors may influence the recipients' knowledge and acceptability, and these included the study period (prior to or after the introduction of the vaccine), the vaccination campaigns in the country, the health insurance coverage, the demographics of participants, etc. Some similarities are seen though: in terms of the differences by the participants' key demographics (i.e. age, rurality, or social-economic status) and the potential predictors of vaccination acceptability (i.e. cost-related issues), the findings were generally the same regardless of the ethnicity of participants and the country in which they lived.

Comparison of methodology

Comparison of knowledge questions: Compared with Western literature, only a few the knowledge questions were used in the Chinese literature, both in surveys among the general population, and also in surveys among health professionals. In Western literature, apart from the basic knowledge (the health consequences of the HPV infection, and the transmission mode), knowledge questions also included:

- Whether wart- and cancer-related HPV types differ
- Whether there is a need for continued Pap screening after vaccination
- Whether poor personal hygiene may lead to HPV infection.

The knowledge of health professionals on these topics may affect the care they deliver and indirectly affect the uptake of screening and the acceptability of the vaccines.

Comparison of acceptability questions: Some studies in the Western literature created hypothetical scenarios for the participants to rate the acceptability [122]. The scenarios included age of the recipient, severity of infection, vaccine efficacy, and the cost of the vaccine. In the Chinese literature, the method used to examine the acceptability were questions such as “Would you vaccinate your daughter or yourself?” regardless of the cost, efficacy, and various health outcomes of the vaccines.

Comparison of attitude questions: Some studies in the Western literature formulated questions regarding attitudes towards the HPV vaccine based on the concept of the Health Belief Model [121]. But these were absent from Chinese literature. Moreover, attitudes on stigma were not explored in Chinese literature. Evidence [187] showed that a biased attitude (a perception of dirtiness and promiscuity for HPV positive people) from health professionals would affect the health care service uptake and create stigma among patients when receiving HPV testing or HPV vaccines. This illustrates the need of education to reduce stigma about HPV infection among health professionals.

Instrument***:*** All but two of the Chinese studies in my review lacked a description of the development of the survey instrument used in the report, whereas studies in the international literature more commonly describe the use of a validated instrument or conducted a pilot study to develop the survey instrument [195-197]. Chinese researchers might have done this and simply not described it in the literature due to the word limit. Because of the logistical issues and limited academic network in China (most Chinese researchers would not reply to unknown academics via Chinese-language email), I did not contact each author to confirm this possibility.

Data analysis: Four studies conducted multivariate analysis to take the confounding (demographics, socio-economic status, etc.) into account. The remainder carried out descriptive or bivariate analysis, ignoring the effect of age, gender, and rurality. Studies in the Western literature were more likely to use multivariate analysis, i.e. logistic regression [198-200], to examine whether there were independent factors influencing the acceptability of the HPV vaccines.

To summarise, the methodological differences between Western and Chinese literature may be explained by the strict rules of reporting and the peer-review process in academic publication in Western literature, as well as the relatively low standard for publishing a paper in China. Failure to contact the authors of studies in my review may have resulted in the loss of some information.

2.6 Conclusion

This is the first systematic review of the Chinese-language literature examining the knowledge of and attitudes towards HPV and vaccination among Chinese populations that I am aware of. It is also the first study to assess the level of knowledge and acceptability from a general geographical perspective—West, North, and South China. Regional variations are commonly used by the government in China to allocate resources rationally. The variation in demographics also offers insight to health professionals and related stakeholders to take account of the potential health inequality and priority when implementing a national vaccination programme.

My review is also among the first to assess the quality of Chinese literature based on a standardised quality assessment tool. Methodological issues raised in the comparison of Western and Chinese literature indicate that Western literature more often has good quality studies. Thus, in the future, Chinese surveys with clear recruitment and sampling frame, theoretical framework, valid instrument, and multivariate analysis should be developed to reduce the potential bias and provide more robust evidence in this field. This review facilitated the next stage of my PhD work, in which I carried out a questionnaire survey in China, seeking to use robust methods throughout.

The key findings of my systematic review are summarised in the box below.

Box. Summary of knowledge of and attitudes towards HPV and vaccination among Chinese

Awareness

A low level of awareness of HPV (<10%) was found:

- in West China
- among Uyghur women adults, rural women adults and teenagers.

A moderate level of awareness of HPV (approximately 30%) was found:

- in North and South China
- among young adults and urban women adults.

A high level of awareness of HPV (>85%) was found:

- among health professionals.

Knowledge

The knowledge that HPV causes cervical cancer and HPV is sexually transmitted are the two most examined issues. The level of knowledge showed a similar trend to awareness.

Acceptability

A low level of acceptability of HPV vaccine (<30%) was reported:

- among health professionals, for daughters.

A moderate level of acceptability of HPV vaccine (50–60%) was reported:

- in South China.

A high level of acceptability of HPV vaccine (>70%) was reported:

- in North China.

Predictors of HPV vaccine

The most examined predictors of HPV vaccine:

- cost of the vaccine
- source through which the vaccine would be offered
- age at vaccination

Table 2-1: Keywords used for literature search

No.	English keywords	Chinese keywords (Pinyin)		
1	HPV	HPV		
2	Human papillomavirus	人乳头瘤病毒 (renrutouliu bingdu)		
3	HPV vaccination	HPV 疫苗 (HPV yimiao)		
4	HPV immunisation	HPV 免疫 (HPV mianyi)		
5	knowledge	知识 (zhishi)		
6	perception	认知 (renzhi)		
7	awareness	知晓 (zhixiao)		
8	attitude	态度 (taidu)		
9	acceptability	接受度 (jieshoudu)		
10	will	意愿 (yiyuan)		
11	health behaviour	健康行为 (jiankangxiangwei)		
Search	#1 AND #5	#2 AND #5	#3 AND #5	#4 AND #5
	#1 AND #6	#2 AND #6	#3 AND #6	#4 AND #6
	#1 AND #7	#2 AND #7	#3 AND #7	#4 AND #7
	#1 AND #8	#2 AND #8	#3 AND #8	#4 AND #8
	#1 AND #9	#2 AND #9	#3 AND #9	#4 AND #9
	#1 AND #10	#2 AND #10	#3 AND #10	#4 AND #10
	#1 AND #11	#2 AND #11	#3 AND #11	#4 AND #11

Table 2-2: The comparison of quality assessment tools

Tools	Key domain	The tool purpose	Ease of use	Development of tool
Cowley's[142]	Y	For systematic review of observation studies, but single use for specific ones	Y	N
Downs' checklist[137]	Y	For critical appraisal of observational studies	Y	Y
EPHPP[139]	Y	For critical appraisal of observational studies	Y	N
Newcastle-Ottawa [140]	Y	For systematic reviews of observational studies	Y	N
Reisch's[144]	N	Specific for critical appraisal of therapeutic studies	N	N
SIGN[143]	Y	The tool purpose is ambiguous and could be used in a few situations, e.g. guideline development, reporting, systematic review, etc.	Y	Y
Zaza's checklist[141]	Y	For systematic reviews of observational studies, specific for case-control and cohort studies	Y	Y

Y: Yes; the tool included the key domain, was easy to use, and showed evidence of development.

N: no; the tool did not include the key domain, was not easy to use, and did not describe development.

Table 2-3: Quality assessment tool for systematic review

	Questions	Yes	No	N/A
Description	1. Was the study population well described (including sample size justification)?			
Sampling	2. Was there a specific sampling frame for the study population?			
	3. Were there specific inclusion/exclusion criteria for all groups?			
	4. Was the study population used as a probability sample?			
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?			
Measurement	6. Were the primary/ secondary outcomes clearly defined?			
	7. Was the measurement method valid?			
	8. Was the measurement method reliable?			
Data analysis	9. Did the researchers conduct statistical testing?			
	10. Did the researchers report which statistical tests were used?			
	11. Were multiple comparisons taken into consideration?			
	12. Were the modelling and multivariate techniques appropriate?			
	13. Was the power calculation provided?			
	14. Was there an assessment of confounding?			
Interpretation of results	15. Did at least 80% of enrolled participants complete the study?			
	16. Did the researchers correct for controllable variables to limit bias appropriately (randomisation, stratification or statistical adjustment)?			
	17. Did the researchers describe all potential bias or unmeasured confounders?			

Adapted from Zaza's checklist [141]

Table 2-4: The scores for each item on the checklist

	Questions	Score	
Description	1. Was the study population well described?	2	2: well described, including demographics (age, gender, etc.) and sample size 1: some population characteristics were missing 0: did not describe population
Sampling	2. Was there a specific sampling frame for the study population?	2	2: sampling frame, including recruitment context (when, where, who, and how) 1: some characteristics were missing 0: did not describe the sampling
	3. Were there specific inclusion/exclusion criteria for all groups?	2	2: sampling criteria, including inclusion and exclusion criteria 1: some criteria were missing 0: did not describe the criteria
	4. Was the study population served as a probability sample?	2	2: described sampling method, and it was a random sample 1: described sampling method, but it was not a random sample 0: did not describe the sampling method
	5. Was there other selection bias (low participation rate, all-volunteer sample, or inappropriate control)?	1	1: no other selection bias 0: there was other selection bias
Measurement	6. Were the primary/secondary outcomes clearly defined?	2	2: outcomes were clearly defined 1: outcomes were defined, but not very clearly 0: outcomes were not described
	7. Was the measurement method valid?	1	1: questions were provided and fulfil the objectives of the study 0: questions were not provided
	8. Was the measurement method reliable?	1	1: reliability test was conducted 0: no reliability test was conducted
Data analysis	9. Did the researchers conduct statistical testing?	1	1: statistical analysis was conduced 0: statistical analysis was not conduced
	10. Did the researchers report which statistical tests were used?	1	1: statistical tests were used 0: statistical tests were not used
	11. Were multiple comparisons taken into consideration?	1	1: multivariate analysis was conducted 0: multivariate analysis was not conducted
	12. Were the modelling and multivariate techniques appropriate?	1	1: multivariate analysis was appropriate 0: multivariate analysis was not appropriate
	13. Was the power calculation provided?	1	1: power calculation was provided 0: power calculation was not provided

Table 2-4: Continued

	Questions	Score	
	14. Was there an assessment of confounding?	1	1: confounding was assessed 0: confounding was not assessed
Interpretation of results	15. Did at least 80% of enrolled participants complete the study?	1	1: the response rate was over 80% 0: the response rate was less than 80%
	16. Did the researchers correct for controllable variables to limit bias appropriately (randomisation, stratification, or statistical adjustment)?	2	2: the researchers corrected the controllable variables and reported the method 1: the researchers did not clearly report the correction of variables 0: the researchers did not correct the variables
	17. Did the researchers describe all potential bias or unmeasured confounders?	1	1: the researchers described potential bias or confounders 0: the researchers did not describe potential bias or confounders

Table 2-5: Characteristics of included studies

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population
Chen J 2011	Zhejiang	2010	123	Urban hospital	Telephone interview with HPV-positive women at home	17-79	HPV-positive women who took the HPV test from March to April in 2010 at one hospital
Cui B 2010	Liaoning	2010	1160	Urban hospital village	Self-administered questionnaire filled in at one room in the selected hospitals and villages	15-59	Outpatients, inpatients, and female relatives of the patients in seven urban hospitals; women residents in the selected villages
Fu FH 2010	Beijing	2008	2952	Urban community	Interview-administered questionnaire conducted by trained researchers	40-95	Women residents in three communities in Shijingshan district from 7 –18April 2008
Fan XF 2011	Xinjiang	2011	242	N/A	Self-administered questionnaire filled in at the same time at one place	28-60	Women with low medical insurance
Fan BJ 2010	Liaoning	2009	962	Urban hospital	Interview-administered questionnaire conducted by the researchers	19-72	Women outpatients selected from a hospital within one year
Feng SW 2010	Zhejiang	2010	1432	Urban and rural hospital	Self-administered questionnaire filled in at selected hospitals	20-50	782 women from urban hospitals, 650 women from rural hospitals within six months
Gao L 2012	Yunnan	2008	2648	Village	Interview- administered questionnaire conducted by the researchers	30-59	Rural women from Linxiang district in Yunnan province
Guzhanuer A 2012)	Xinjiang	2008	560	Village	Interview- administered questionnaire conducted by the researchers	N/A	90% Uyghur men were from rural regions, 10% Uyghur men were from urban regions in Hetian district
Gulinuer A 2010	Xinjiang	2006	248	Urban hospital	Self-administered questionnaire filled in at the selected hospital by the gynaecologists	20-65	Women outpatients between March and June in 2006 at Bozhou hospital in Xinjiang
Guzhalinuer A 2007	Xinjiang	2006	400	Urban hospital	Self-administered questionnaire filled in at five hospitals by the gynaecologists	23-76	Uyghur Cervical cancer patients in five hospitals in Xinjiang
Huang GF 2011	Guangdong	2008	196	Urban hospital	Self-administered questionnaire filled in at the selected hospital	20-58	Women during a certain time period at the selected hospital
He M 2011	Seven regions of China	2007–2009	9865 women, 780 health professionals	Urban hospital	Self-administered questionnaire filled in at 14 hospitals in seven regions of China	18-82	Women outpatients and health professionals outpatients at 14 hospitals from 2007 to 2009
He X 2010	Henan	2009	2102	College	Self-administered questionnaire filled in during class	16-26	1093 female and 1009 male students from two universities in 2010
Jiang SY 2010	Shanghai	2007–2009	944	Urban community	Self-administered questionnaire filled in at one place in the community	20-65	Women residents in one community of Hong Kou district of Shanghai city in 2010

Table 2-5: continued

Study	Study location	Year of study	No. of participants	Study setting	Study instrument	Age (years)	Study population
Lu KN 2008	Beijing	2008	104	Urban hospital	Self-administered questionnaire filled in at the selected hospitals	19-69	Outpatients and inpatients selected from 3 hospitals from Sep to Dec in 2007
Li J 2008	Beijing	2008	1013	Urban community	Interview-administrated questionnaire conducted by the trained researchers	15-54	Women residents in Zhanlanlu community of Beijing city from June of 2006 to June of 2007
Li JM 2008	Guangdong	2008	304	Urban community	Self-administered questionnaire filled in at one place in the community	18-60	Women residents in one community in Baoan district of Shenzhen city
Li XP 2007	Zhejiang	2007	300	Urban community	Self-administered questionnaire filled in at one place in the community	20-50	Women residents in Nanpu community of Wenzhou city
Li J 2011	Liaoning	2011	160	Urban and rural hospital	Self-administered questionnaire filled in at one place in the hospital	36.6±9.6	Doctors and government officials
Li CT 2011	Xinjiang	2011	960	N/A	Self-administered questionnaire	20-39	Women residents in Tianshan district in Urumqi city
Liu ZH 2012	Hunan	2011	848	High school	Self-administered questionnaire filled in during class	14-18	396 male and 452 female high school students in Xiangtan city
Long XE	Zhejiang	N/A	286	College	Self-administered questionnaire filled in during class	>18	Medical testing major students from selected college
Ma D 2012	Hebei	2011	198	Urban hospital	Self-administered questionnaire filled in at the selected hospital	20-54	49 doctors and 149 nurses from selected hospital in Tangshan city
Ma D 2010	Beijing	2010	249	Urban community and hospital	Self-administered questionnaire filled in at one place	30-55 community; 16-56 outpatients	100 community women residents from a selected community and 149 women outpatients from a selected hospital
Ren CL 2011	Xinjiang	2010	1005	N/A	Interview-administered questionnaire conducted by researcher	18-58	355 Han, 328 Uyghur, and 322 Hui women from Malan district in Xinjiang region
Song D 2007	Shanxi	2007	957	Village	Self-administered questionnaire filled in at selected villages	15-54	Women from 26 villages in Xiangyuan county in Shanxi province
Sun J 2010	Liaoning	2010	310	Urban hospital	Self-administered questionnaire filled in at selected hospital	21-60	Women from one hospital in Dalian from Feb to Mar in 2010
Shi YY 2011	Heilongjiang	2010	1200	Village and urban hospital	Self-administered questionnaire filled in by health professional researchers	20-60	600 women residents from three selected villages and 600 women outpatients from a selected hospital

Table 2-5: continued

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population
Wang HQ 2011	Hebei	2011	257	Urban hospital	Self-administered questionnaire filled in at the four selected hospitals	20-53	Obstetricians and Gynaecologists from four hospitals in Tangshan city
Wen LZ 2010	Xinjiang	2009	400	Urban hospital	Self-administered questionnaire filled in at the selected hospital	22-48	Women outpatients at one hospital selected from Jan to June in 2009
Wang QL 2011	Sichuan	2010	886	Village	Interview-administrated questionnaire conducted by the trained researchers	41.9 (mean)	Women residents from 3 counties in north Sichuan mountain areas
Wu Y 2011	Zhejiang	2010	489	N/A	Self-administered questionnaire filled in at one place	>15	Women residents in Hangzhou city
Wang XM 2012	Shanxi	2010	2269	Urban hospital and village	Interview-administered questionnaire by researcher	25-73	341 urban women residents and 1928 rural women residents
Xiamixinuer A 2010	Xinjiang	2004–2006	245	Urban hospital	Self-administered questionnaire filled in at the selected hospitals by the gynaecologists	23-85	Uyghur cervical cancer patients selected from five hospitals from Jan of 2004 to Jul of 2006
Xiao W 2010	Beijing	2008	368	Urban hospital	Self-administered questionnaire filled in at the selected hospital	21-74	Women outpatients selected from one hospital from Jan to Apr in 2008
Xing YX	Qinghai	2009	200	N/A	Self-administered questionnaire filled in by local doctors	18-63	136 Tibetan women residents and 64 Han women population
Xu CY 2010	Beijing	2007–2008	6339	Urban and rural community	Self-administered questionnaire filled in at one place in the community	25-54	Women residents from four districts of city, four districts of inner suburbs and four districts of outer suburbs
Xu LN	Beijing, Tianjin, Shanxi	2009	1666	Urban hospital and village	Self-administered questionnaire filled in at one place in the hospital and selected villages	15-59	640 from urban residents and 1026 from rural residents in the three provinces from June to November in 2009
Xie Y 2011	Sichuan	2010	2000	Village	Interview-administered questionnaire at selected villages	30-59	Women from 3 counties in August in 2010
Ye JR 2011	Guangdong	2010	1120	Village	Self-administered questionnaire filled in at selected villages	23-51	560 married women from two villages from January of 2010 to January of 2011
Zhang LJ 2009	Guangdong	2006–2007	100	Urban hospital	Self-administered questionnaire filled in at one place in the hospital	18-54	Women patients from on hospital from December of 2006 to September of 2007
Zhao DJ 2010	Shanghai	2009	997	Urban community	Self-administered questionnaire filled in at one place	16-54	Women residents in two selected communities in Shanghai

Table 2-5: continued

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population
Zhou JY 2010	Beijing	2008	2000	Urban and rural community	Self-administered questionnaire filled in at one place	30-59	Women residents in urban and rural community from April to December in 2008
Zhou LX 2011	Guangdong	2010	752	Urban community and hospital	Interview-administered questionnaire at selected community and hospital	16-55	Women residents from selected community and women outpatients from selected hospital
Zhou Y 2010	Hunan	2009	207	College	Self-administered questionnaire filled in during class	17-21	64 male and 143 female first-year students from selected college
Zhou Y 2012	Hunan	2009	2239	College	Self-administered questionnaire filled in the dormitory	17-25	1428 male and 865 female students from selected college
Zhou Y 2011	Shanxi	2010	500	Village	Interview-administered questionnaire at selected village	17-59	Women residents from selected county in Shanxi province

Table 2-6: Main results of included studies in the comparison of study quality and wording of questions

Study	Quality	Awareness (%)	Wording of questions	Knowledge (%) (STI)	Wording of questions	Knowledge (%) (CC)	Wording of questions	Acceptance (%)	Wording of questions
Cui B 2010	Good	17	Have you heard of HPV			6-9 (rural-urban)	HPV can lead to CC	64-68 (rural-urban)	Are you willing to be vaccinated
Feng SW 2010	Good	27-39 (rural-urban)	Have you heard of HPV	38-50 (rural-urban)	HPV is sexually transmitted	40-49 (rural-urban)	HPV can lead to CC		
He M 2011	Good	33	Have you heard of HPV			90 (HPs)	HPV is the essential element of CC	70-72 (urban F-HPs)	Are you willing to be vaccinated
Jiang SY 2010	Good	25-42	N/A			34	HPV is the main cause of CC		
Li J 2008	Good	31	Have you heard of HPV			52	When referring to HPV, your first thought is…	76	Are you willing to be vaccinated
Li JM 2008	Good			55	HPV is sexually transmitted	31	HPV is the main cause of CC		
Ma D 2010	Good			15-29	HPV is sexually transmitted	24-33	HPV is the main cause of CC		
Sun J 2010	Good			20	HPV is sexually transmitted	24	HPV is the main cause of CC		
Shi YY 2011	Good					13	HPV is related with CC		
Wang XM 2012	Good			6-24 (rural-urban)	HPV is sexually transmitted				
Xu LN	Good	12-33 (rural-urban)	Have you heard of HPV			63	HPV can lead to CC	73-79 (rural-urban)	Are you willing to be vaccinated
Fu FH 2010	Fair	16	Do you know what HPV is			7	When referring to HPV, your first thought is…		
Fan BJ 2010	Fair	24	Have you heard of HPV			57	When referring to HPV, your first thought is…	88	Are you willing to be vaccinated
Gao L 2012	Fair					3 (rural)	HPV is the essential element of CC		
Gulinuer A 2010	Fair	7 (Uyghur)	Do you know what HPV is			14 (Uyghur)	HPV is related with CC		
Huang GF 2011	Fair							32	Are you willing to be vaccinated
He X 2010	Fair	37-50 (F-M)	Have you heard of HPV	60-76 (F-M)	HPV is sexually transmitted	53-55 (M-F)	HPV can lead to CC		

STI: sexually transmitted infection; CC: cervical cancer.

Table 2-6: Continued

Study	Quality	Awareness (%)	Wording of questions	Knowledge (%) (STI)	Wording of questions	Knowledge (CC) (%)	Wording of questions	Acceptance (%)	Wording of questions
Lu KN 2008	Fair	46	Have you heard of HPV						
Li J 2011	Fair	44-89 (GOs-HPs)				30-79 (GOs-HPs)		74-81 (GOs-HPs)	
Li CT 2011	Fair	11	Do you know what HPV is						
Liu ZH 2012	Fair	10	Have you heard of HPV	16	HPV is sexually transmitted	19	HPV can lead to CC		
Ma D 2012	Fair	77-92 (HPs)	Have you heard of HPV	67-88 (HPs)	HPV is sexually transmitted	50-82	HPV is the essential element of CC	23-35 (HPs)	
Ren CL 2011	Fair					5,12,21 (Uyghur, Hui, Han)	HPV is the main cause of CC		
Song D 2007	Fair	6 (rural)	Have you heard of HPV			35 (rural)	When referring to HPV, your first thought is…	97 (rural)	Are you willing to be vaccinated
Wang HQ 2011	Fair	92 (HPs)	Have you heard of HPV	92 (HPs)	HPV is sexually transmitted	84 (HPs)	HPV is the essential element of CC		
Wu Y 2011	Fair							48	Are you willing to be vaccinated
Xiamixinuer A 2010	Fair	0 (Uyghur)	Do you know what HPV is	0 (Uyghur)	HPV is sexually transmitted	0 (Uyghur)	HPV is a risk factor of CC		
Xiao W 2010	Fair	46	Have you heard of HPV					73	Are you willing to be vaccinated
Xing YX	Fair	2 (Han, Tibetan)	Do you know what HPV is						
Xu CY 2010	Fair					27	HPV is a risk factor of CC		
Xie Y 2011	Fair			1 (rural)	HPV is sexually transmitted				
Ye JR 2011	Fair	4 (rural)	Do you know what HPV is			3 (rural)	HPV is related with CC		
Zhao DJ 2010	Fair	21	Have you heard of HPV					66	Are you willing to be vaccinated

STI: sexually transmitted infection; CC: cervical cancer.

Table 2-6: Continued

Study	Quality	Awareness (%)	Wording of questions	Knowledge (%) (STI)	Wording of questions	Knowledge (CC) (%)	Wording of questions	Acceptance (%)	Wording of questions
Zhou JY 2010	Fair					16	HPV is the essential element of CC		
Zhou LX 2011	Fair	36-46	Have you heard of HPV						
Zhou Y 2012	Fair	17-21 (F-M)	Have you heard of HPV	46	HPV is sexually transmitted	75	HPV can lead to CC		
Chen J 2011	Poor					70 (HPV P)	HPV is related with CC		
Fan XF 2011	Poor			25	HPV is sexually transmitted	22	HPV is the main cause of CC		
Guzhanuer A 2012	Poor	0 (Uyghur M)	Do you know what HPV is			0 (Uyghur M)	HPV is the main cause of CC		
Guzhalinuer A 2007	Poor	0 (Uyghur)	Do you know what HPV is			0 (Uyghur)	HPV is related with CC		
Li XP 2007	Poor	8	Have you heard of HPV	12	HPV is sexually transmitted	22	HPV is related with CC		
Long XE	Poor	3-74	Do you know what HPV is	81	HPV is sexually transmitted				
Wen LZ 2010	Poor	45	Do you know what HPV is			30	HPV is related with CC		
Wang QL 2011	Poor					0.2 (rural)	HPV is related with CC		
Zhang LJ 2010	Poor			28	HPV is sexually transmitted	11	HPV is related with CC		
Zhou Y 2010	Poor	18	Have you heard of HPV	30	HPV is sexually transmitted	86	HPV can lead to CC		
Zhou Y 2011	Poor	12 (rural)	Have you heard of HPV			70 (rural)	HPV can lead to CC	82 (rural)	Are you willing to be vaccinated

STI: sexually transmitted infection; CC: cervical cancer

Table 2-7: Scores of each items of each individual study based on the scoring standard in the checklist

Quality	Study	Score	Have the items of the checklist in the quality assessment been fulfilled or not																
			SP*	SF*	I/E* criteria	P* sample	SB*	SO*	VM*	RM*	ST* used	ST* report	MC*	MT*	PC*	C*	RR*	CC*	bias
Good	Feng SW 2010	22	2	2	2	2	1	2	1	1	1	1	1	1	1	1	0	2	1
	Cui B 2010	20	2	2	2	2	1	2	1	0	1	1	0	0	1	1	1	2	1
	Xu LN	20	2	2	2	2	1	2	1	0	1	1	1	1	1	1	1	1	0
	Jiang SY 2010	19	2	2	2	2	1	2	1	0	1	1	0	0	1	1	1	2	0
	Li J 2008	19	2	2	2	2	1	2	1	0	1	1	0	0	1	1	0	2	1
	Li JM 2008	19	2	2	2	2	1	2	1	0	1	1	0	0	1	1	0	2	1
	Shi YY 2011	19	2	2	2	2	1	2	1	0	1	1	0	0	1	1	1	1	0
	He M 2011	18	2	2	0	2	1	2	1	0	1	1	1	1	1	1	0	1	1
	Ma D 2010	18	2	2	2	1	1	2	1	1	1	1	0	0	1	1	0	2	0
	Sun J 2010	18	2	2	2	1	1	2	1	1	1	1	1	1	1	0	1	0	0
	Wang XM 2012	18	2	2	2	2	1	2	1	0	1	1	0	0	1	1	0	2	0
Fair	Fan BJ 2009	17	2	2	0	2	1	2	1	0	1	1	0	0	1	1	1	2	0
	Gao L 2012	17	2	2	1	0	0	2	1	0	1	1	1	1	1	1	0	2	1
	He X 2010	17	2	2	0	2	1	2	1	0	1	1	0	0	1	1	1	2	0
	Liu ZH 2012	17	2	2	0	2	1	2	1	1	1	1	1	1	1	0	1	0	0
	Wang HQ 2011	17	2	2	0	2	1	2	1	0	1	1	0	0	1	1	1	2	0
	Zhou Y 2012	17	2	2	0	2	1	2	1	0	1	1	0	0	1	1	1	2	0
	Li CT 2011	17	2	1	2	1	1	2	1	0	1	1	0	0	1	1	0	2	0
	Lu KN 2008	16	2	2	0	1	1	2	1	0	1	1	0	0	1	1	1	2	0
	Li J 2011	16	2	1	1	2	1	2	1	0	1	1	0	0	1	0	1	2	0
	Ma D 2012	16	2	2	0	1	1	2	1	1	1	1	0	0	1	1	1	1	0
	Xu CY 2009	16	2	2	2	2	1	2	1	0	1	1	0	0	1	0	1	0	0
	Xie Y 2011	16	2	2	2	2	1	2	1	0	1	1	0	0	1	0	1	0	0
	Ye JR 2011	16	2	2	2	2	1	2	1	0	1	1	0	0	1	0	1	0	0
	Gulinuer A 2009	15	2	2	1	0	1	2	1	0	1	1	0	0	1	1	0	2	0
	Ren CL 2011	15	2	1	2	1	1	2	1	0	1	1	0	0	1	0	0	2	0
	Song D 2007	15	2	2	2	0	1	2	1	0	1	1	0	0	1	1	1	0	0
	Wu Y 2011	15	2	0	0	2	1	2	1	0	1	1	0	0	1	1	1	2	0

*Abbreviations of words are used due to the limited space in the table.

SP: study population; SF: Sampling frame; I/E: inclusion/exclusion; P: probability; SB: selection bias; VM: valid measurement; RM: reliable measurement; ST: statistical testing; MC: Multiple comparison; MT: Multivariate techniques; PC: Power calculation; C: confounding; RR: response rate; CC: correct for controllable variables

Table 2-7: continued

Quality	Study	Score	Have the items of the checklist in the quality assessment been fulfilled or not																
			SP*	SF*	I/E* criteria	P* sample	SB*	SO*	VM*	RM*	ST* used	ST* report	MC*	MT*	PC*	C*	RR*	CC*	bias
Good	Xiao W 2009	15	2	2	0	0	1	2	1	0	1	1	0	0	1	1	1	2	0
	Zhou JY 2010	15	2	1	2	2	1	2	1	0	1	1	0	0	1	0	1	0	0
	Zhou LX 2011	15	2	1	2	2	1	2	1	0	1	1	0	0	1	0	1	0	0
	Fu FH 2010	14	2	2	1	0	1	2	1	0	1	1	0	0	1	1	1	0	0
	Huang GF 2011	14	2	1	2	0	1	2	0	0	1	1	0	0	1	1	0	2	0
	Xiamixinuer A 2009	14	2	2	1	0	1	2	1	0	1	1	0	0	0	1	0	2	0
	Xing YX	14	2	2	0	0	1	2	1	0	1	1	0	0	1	1	0	2	0
	Zhao DJ 2010	14	2	2	0	2	1	2	1	0	1	1	0	0	1	1	0	0	0
Poor	Chen J 2011	13	2	2	1	0	1	2	1	0	1	1	0	0	1	0	1	0	0
	Zhang LJ 2009	13	2	2	2	0	1	2	1	0	1	1	0	0	1	0	0	0	0
	Guzhanuer A 2012	12	1	2	1	0	0	2	1	0	1	0	0	0	1	1	0	2	0
	Wang QL 2011	12	2	2	0	2	1	2	1	0	1	1	0	0	0	0	0	0	0
	Zhou Y 2010	12	2	2	0	0	1	2	1	0	1	1	0	0	1	0	1	0	0
	Fan XF 2011	11	2	0	2	0	1	2	1	0	1	1	0	0	1	1	1	0	0
	Li XP 2007	11	2	2	0	0	1	2	1	0	1	1	0	0	1	0	0	0	0
	Wen LZ 2009	11	2	2	0	0	1	2	1	0	1	1	0	0	1	0	0	0	0
	Guzhalinuer A 2007	10	2	2	1	0	1	2	1	0	1	0	0	0	0	0	0	0	0
	Zhou Y 2011	10	2	0	0	0	1	2	1	0	1	1	0	0	1	1	0	0	0
	Long XE	8	1	1	0	0	1	2	1	0	1	0	0	0	0	0	1	0	0

*Abbreviations of words are used due to the limited space in the table.

SP: study population; SF: Sampling frame; I/E: inclusion/exclusion; P: probability; SB: selection bias; VM: valid measurement; RM: reliable measurement; ST: statistical testing; MC: Multiple comparison; MT: Multivariate techniques; PC: Power calculation; C: confounding; RR: response rate; CC: correct for controllable variables

Table 2-8: Quality level of included studies

Scores	Number of studies	Quality of studies
18-23	11	Good
14-17	25	Fair
8-13	11	Poor

Table 2-9: Study location, quality, and sample size

Region of China	Study quality	Study	Study location	Sample size (descending in each group)
North China	Good	Wang XM et al 2012	Shanxi	2269
		Xu LN et al	Beijing, Tianjin, Shanxi	1666
		Cui B, 2010	Liaoning	1160
		Shi YY, 2011	Heilongjiang	1200
		Li J et al, 2008	Beijing	1013
		Sun J, 2010	Liaoning	310
		Ma D et al, 2010	Beijing	249
	Fair	Xu CY et al, 2009	Beijing	6339
		Fu FH et al, 2010	Beijing	2952
		He X et al, 2010	Henan	2102
		Zhou JY et al, 2010	Beijing	2000
		Song D, 2007	Shanxi	957
		Fan BJ, 2009	Liaoning	962
		Xiao W et al, 2009	Beijing	368
		Wang HQ et al, 2011	Hebei	257
		Ma D et al, 2012	Hebei	198
		Li J, 2011	Liaoning	160
		Lu KN, 2008	Beijing	104
	Poor	Zhou Y et al, 2011	Shanxi	500
South China	Good	Feng SW, 2010	Zhejiang	1432
		Jiang SY et al, 2010	Shanghai	944
		Li JM et al, 2008	Guangdong	304
	Fair	Zhou Y et al, 2012	Hunan	2239
		Ye JR et al, 2011	Guangdong	1120
		Zhao DJ et al, 2010	Shanghai	997
		Liu ZH et al, 2012	Hunan	848
		Zhou LX et al, 2011	Guangdong	752
		Wu Y et al, 2011	Zhejiang	489
		Huang GF et al 2011	Guangdong	196
	Poor	Li XP et al, 2007	Zhejiang	300
		Long XE et al	Zhejiang	286
		Zhou Y et al, 2010	Hunan	207
		Chen J et al, 2011	Zhejiang	123
		Zhang LJ et al, 2009	Guangdong	100
West China	Fair	Gao L et al, 2012	Yunnan	2648
		Xie Y et al, 2011	Sichuan	2000
		Ren CL et al, 2011	Xinjiang	1005
		Li CT et al, 2011	Xinjiang	960
		Gulinuer A et al, 2009	Xinjiang	248
		Xiamixinuer A et al, 2009	Xinjiang	245
		Xing YX et al	Qinghai	200
	Poor	Wang QL et al, 2011	Sichuan	886
		Guzhanuer A et al, 2012	Xinjiang	560
		Guzhalinuer A et al, 2007	Xinjiang	400
		Wen LZ et al, 2009	Xinjiang	400
		Fan XF et al, 2011	Xinjiang	242

Table 2-10: Awareness and knowledge differences between urban and rural adult women

Region of China	Study quality	Study	Study location	Awareness %	Knowledge of CC* %	Knowledge of STI* %
Urban adult women						
North China	Good	Xu LN et al	Beijing, Tianjin, Shanxi	33		
		Li J et al, 2008	Beijing	31	52	
		Wang XM et al 2012	Shanxi	24		
		Cui B, 2010	Liaoning	17	9	
		Sun J, 2010	Liaoning		24	20
		Ma D et al, 2010	Beijing		28	22
	Fair	Lu KN, 2008	Beijing	46		
		Xiao W et al, 2009	Beijing	46		
		Fan BJ, 2009 88	Liaoning	24	57	
		Fu FH et al, 2010	Beijing	16	7	
South China	Good	Feng SW, 2010	Zhejiang	39	40	50
		Jiang SY et al, 2010	Shanghai	34	34	
		Li JM et al, 2008	Guangdong		31	55
	Fair	Zhou LX et al, 2011	Guangdong	41		
		Zhao DJ et al, 2010	Shanghai	21		
	Poor	Li XP et al, 2007	Zhejiang	8	22	12
		Zhang LJ et al, 2009	Guangdong		11	28
West China	Fair	Li CT et al, 2011	Xinjiang	11		
	Poor	Wen LZ et al, 2009	Xinjiang	45	30	
Rural women adults						
North China	Good	Cui B, 2010	Liaoning	17	6	
		Xu LN et al	Beijing, Tianjin, Shanxi	12		
		Wang XM et al 2012	Shanxi	6		
	Fair	Song D, 2007	Shanxi	6	35	
	Poor	Zhou Y et al, 2011	Shanxi	12	70	
South China	Good	Feng SW, 2010	Zhejiang	27	49	38
	Fair	Ye JR et al, 2011	Guangdong	4	3	
West China	Fair	Gao L et al, 2012	Yunnan		3	
		Xie Y et al, 2011	Sichuan			1
	Poor	Wang QL et al, 2011	Sichuan		0.2	

*CC: cervical cancer; STI: sexually transmitted infection

Table 2-11: Participants' age, ethnicity, health professionals

Region of China	Study quality	Study	Study location	Awareness %	Knowledge of CC** %	Knowledge of STI** %
Uyghur adult women						
West China	Fair	Gulinuer A et al, 2009	Xinjiang	7	14	
		Xiamixinuer A et al, 2009	Xinjiang	0	0	0
	Poor	Guzhalinuer A et al, 2007	Xinjiang	0	0	
Teenagers (14-18 years)						
South China	Fair	Liu ZH et al, 2012	Hunan	10	19	16
Young adults (16-26 years)						
North China	Fair	He X et al, 2010	Henan	37 (F*)	55 (F*)	60 (F*)
				50 (M*)	53 (M*)	76 (M*)
South China	Fair	Zhou Y et al, 2012	Hunan	21 (M)	75	46
				17 (F)		
	Poor	Zhou Y et al, 2010	Hunan	18	86	30
Health professionals						
North China	Fair	Li J, 2011	Liaoning	89	79	
		Ma D et al, 2012	Hebei	85	66	78
		Wang HQ et al, 2011	Hebei	92	84	92

*F: female; M: male. **CC: cervical cancer; STI: sexually transmitted infection

Table 2-12: The acceptability of HPV vaccines among the general population and health professionals

Region of China	Study quality	Study	Study location	Acceptability of GP*		Acceptability of HPs*	
				Oneself %	Daughter %	Oneself %	Daughter %
North China	Good	Cui B, 2010	Liaoning	66			
		Li J et al, 2008	Beijing	76	63		
		Xu LN et al	Beijing, Tianjin, Shanxi	77			
	Fair	Xiao W et al, 2009	Beijing	73	75		
		Song D, 2007	Shanxi	97	97		
		Fan BJ, 2009	Liaoning	88			
		Ma D et al, 2012	Hebei			34	28
		Li J, 2011	Liaoning			74	
	Poor	Zhou Y et al, 2011	Shanxi	82	63		
South China	Fair	Wu Y et al, 2011	Zhejiang	48	64		
		Huang GF et al 2011	Guangdong	32			
		Zhao DJ et al, 2010	Shanghai	66	54		

*GP: general population; HPs: health professionals

Table 2-13: Factors that would influence the acceptability of HPV vaccines

Region of China	Study quality	Study	Study location	Study population	The source for the vaccine people would prefer if it is offered			The cost people agree or would like to pay		Have not been used on a large scale %	No perceived risk of CC** %
					Government %	Medical institutions %	Large drug companies %	Government cover all the cost %	Would like to pay < ¥100 %		
North China	Good	Li J et al, 2008	Beijing	GP*	55.8	41.8	2.0	57.1		61.5	58.2
	Fair	Fan BJ, 2009	Liaoning	GP*	55.4			46.6			
		Song D, 2007	Shanxi	GP*			60.7	67.2			
		Xiao W et al, 2009	Beijing	GP*	71.0	25.8	2.9	55.8	84.2	31.9	37.2
		Wang HQ et al, 2011	Hebei	HPs*				54.5			
South China	Fair	Wu Y et al, 2011	Zhejiang	GP*	82.0				71.2 pay <¥500	12.3	4.9
		Zhao DJ et al, 2010	Shanghai	GP*	65.0	32.6	1.9		93.9	63.9	68.6
North, South, West China	Good	He M et al, 2011	Seven regions of China	GP*	56.2	38.7	5.0	41.5		43.6	26.2
				HPs*	40.4	45.3	13.7	35.8		39.8	38.3

*GP: general population; HPs: health professionals
**CC: cervical cancer
All the data presented in the table refers to the proportion of respondents who chose the option.

Figure 2-1: Flow diagram of selection of quality assessment tools

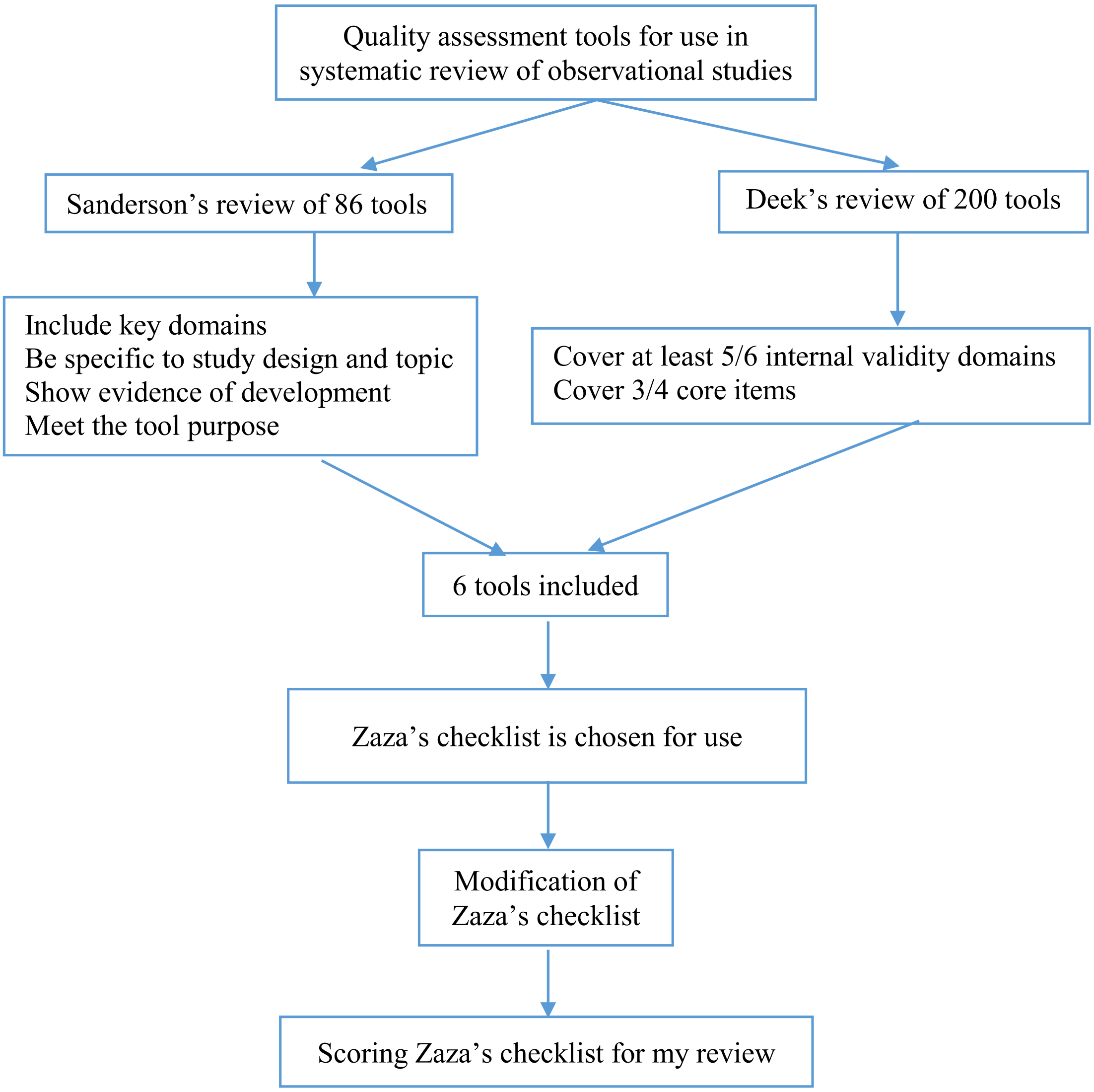


Figure 2-2: PRISMA diagram of my systematic review

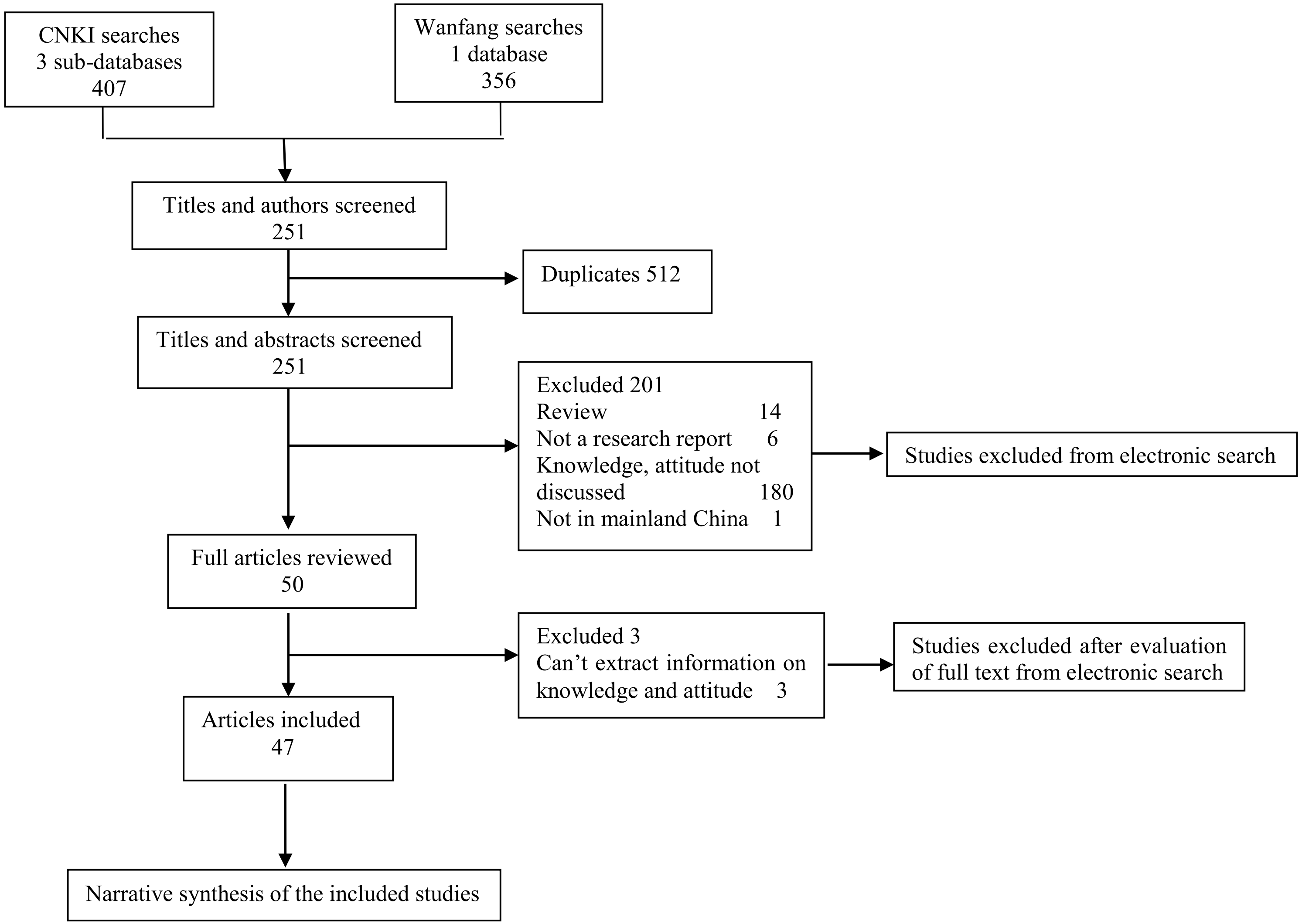


Figure 2-3: The number of studies (and percentage) that meet the criteria in the quality assessment

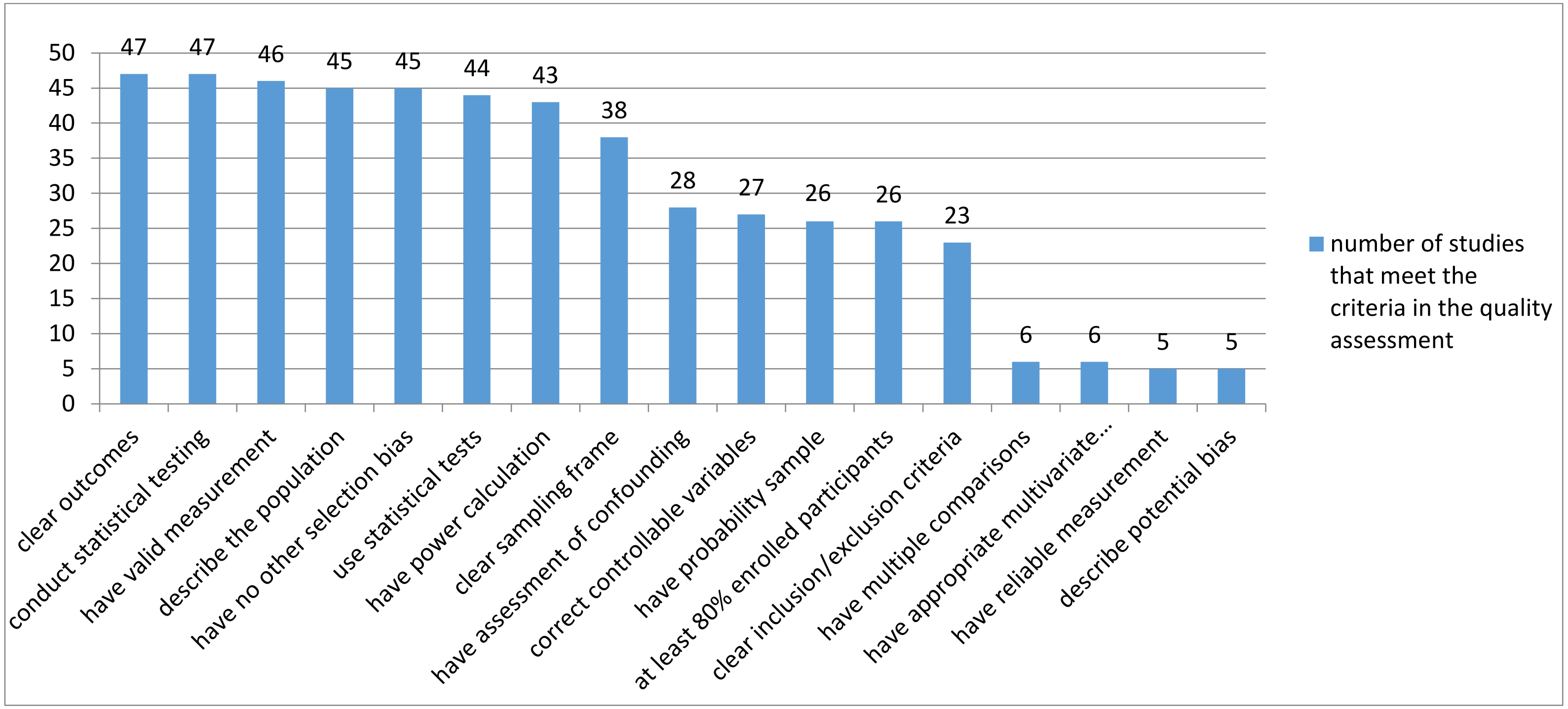
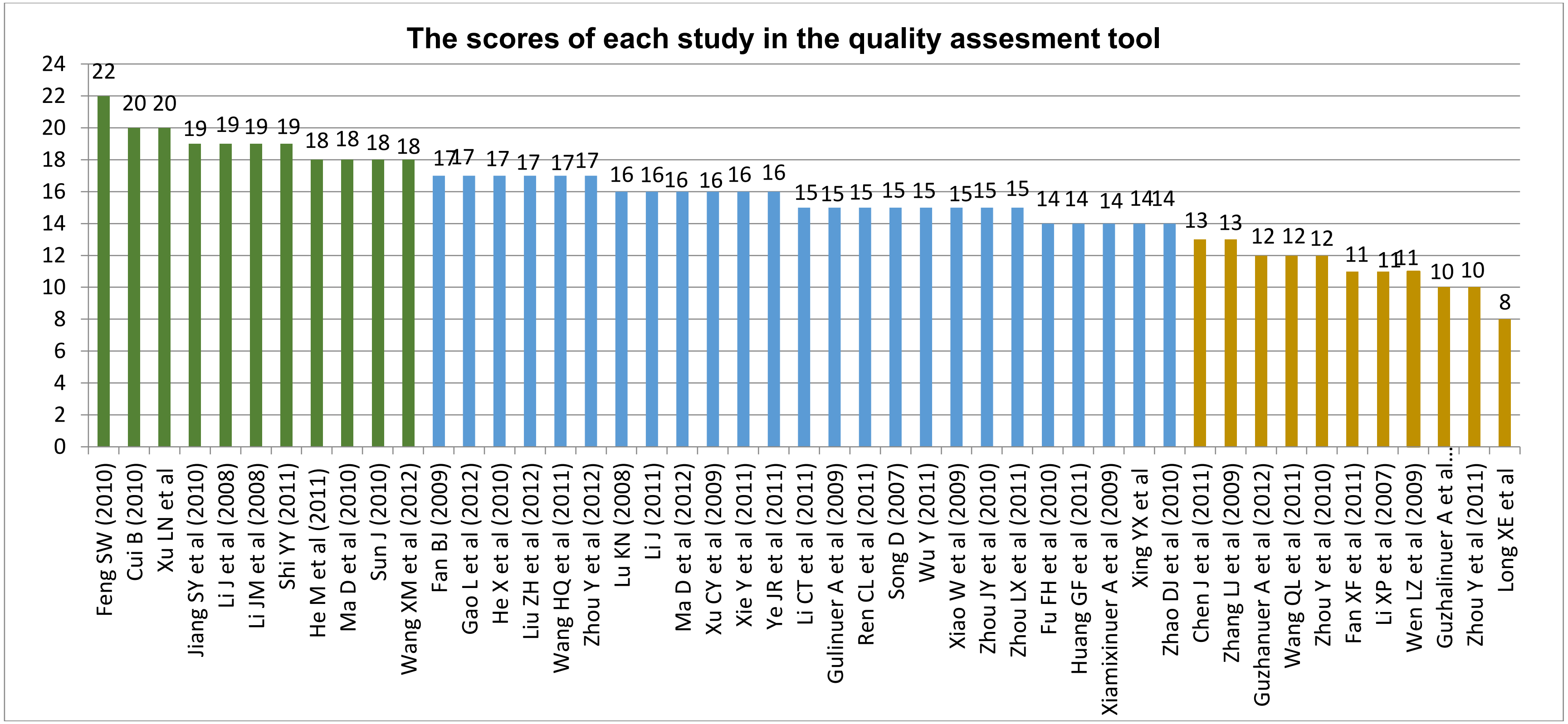


Figure 2-4: The scores of each study in the quality assessment tool



Green: good quality; **Blue**: fair quality; **Yellow**: poor quality

Figure 2-5: Distribution of the number of participants in the included studies in different parts of China

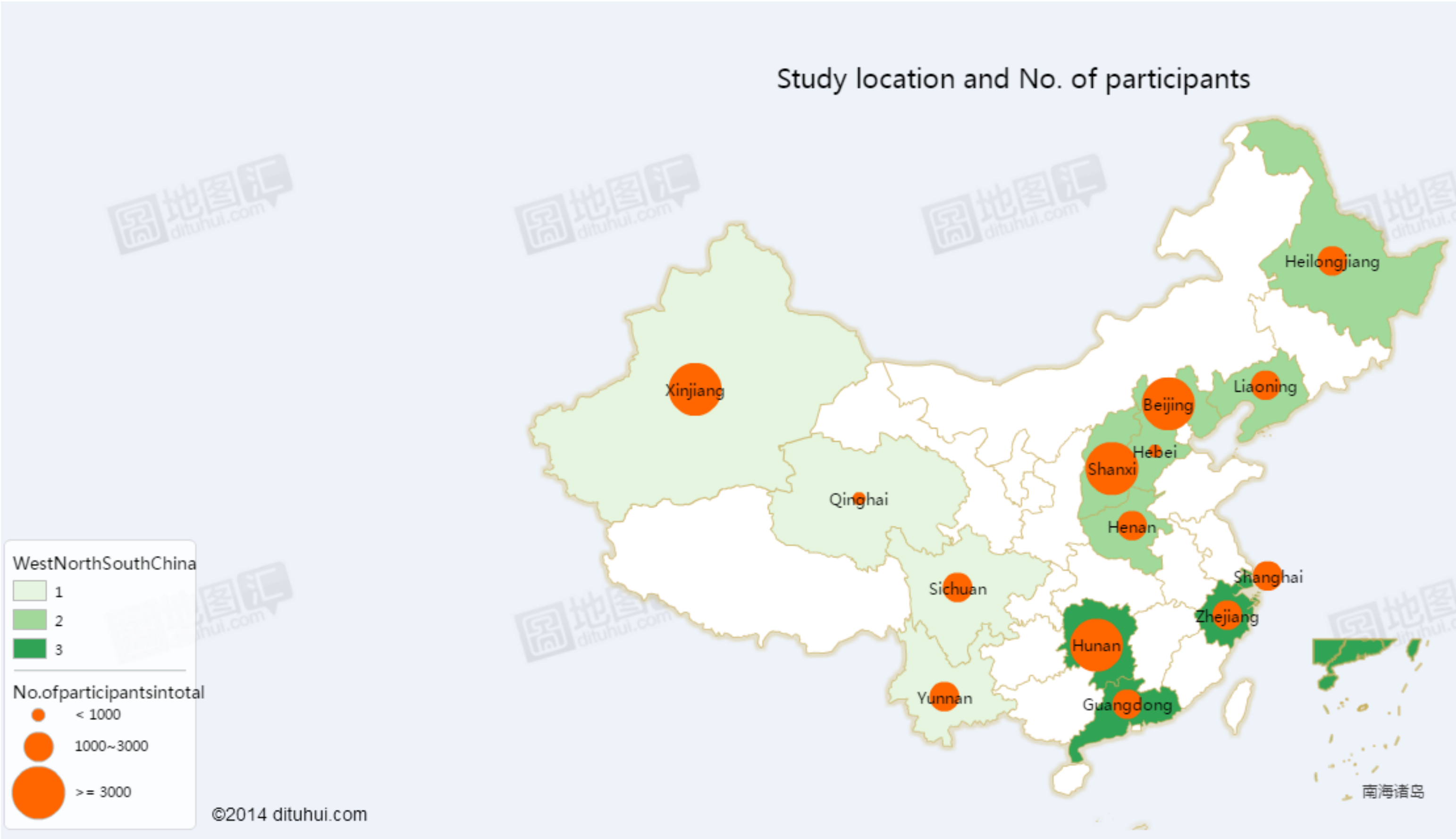


Figure 2-6: Distribution of the number of good quality studies in different parts of China

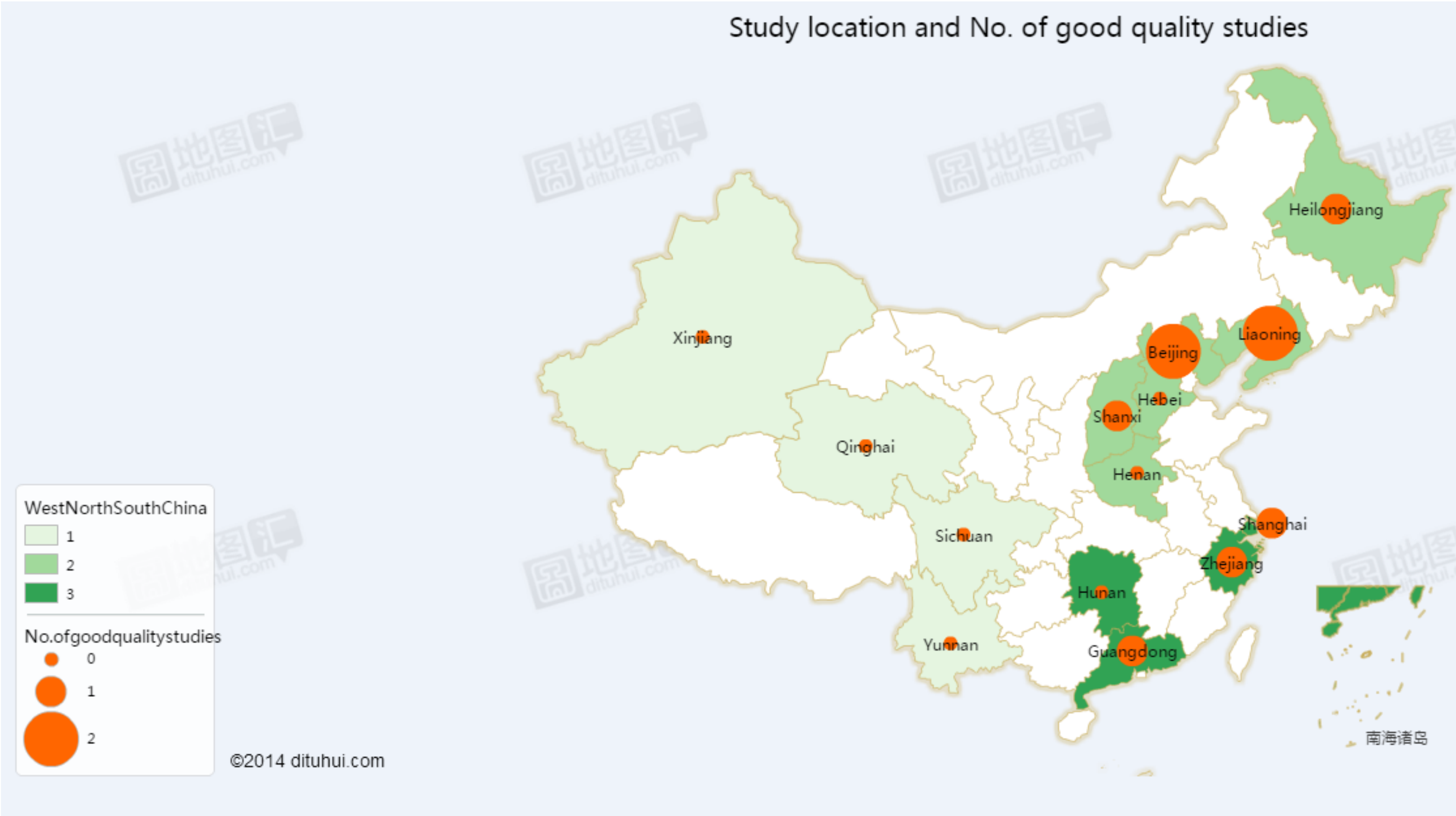


Figure 2-7: Distribution of the number of included studies in different parts of China

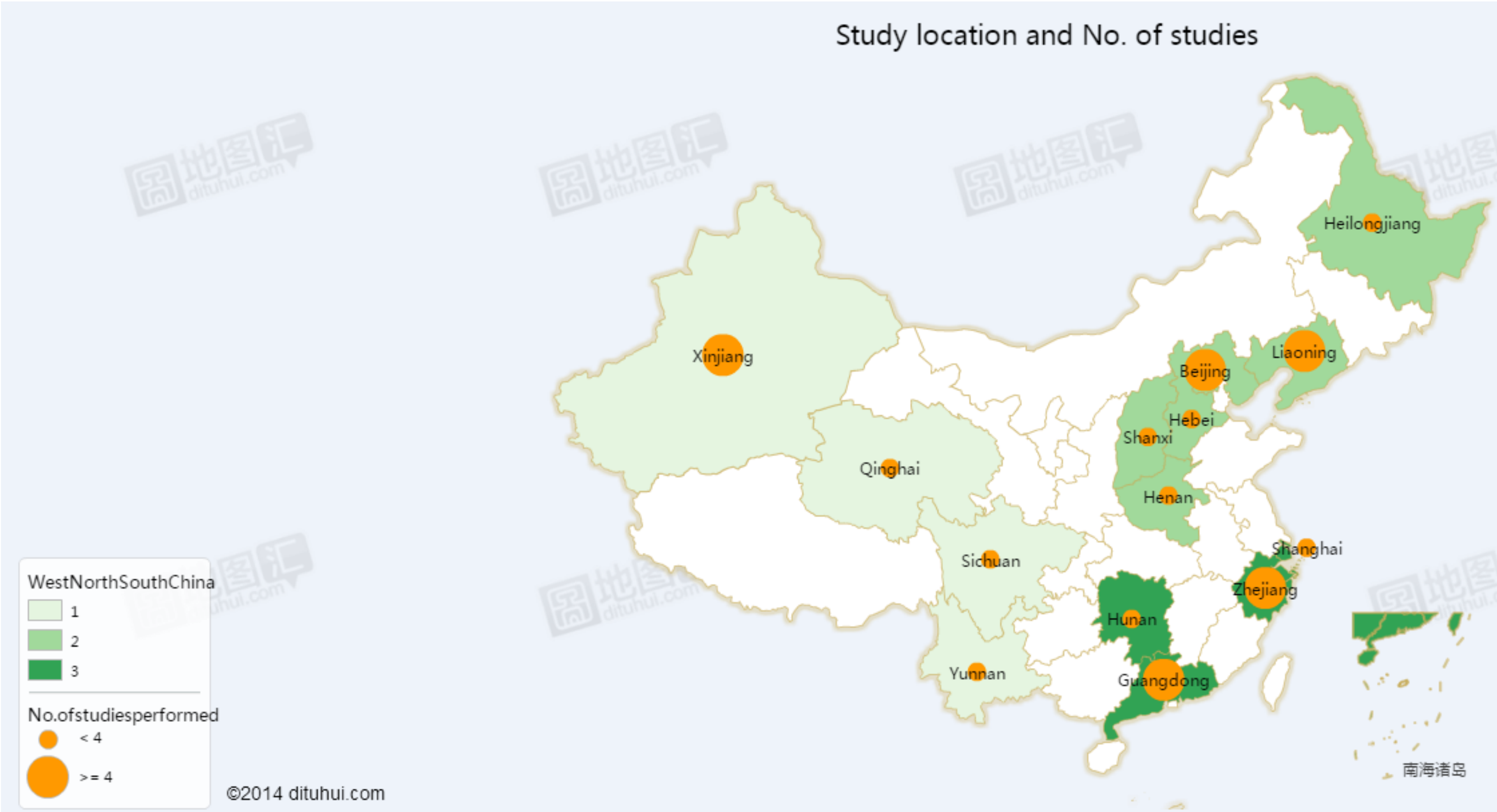
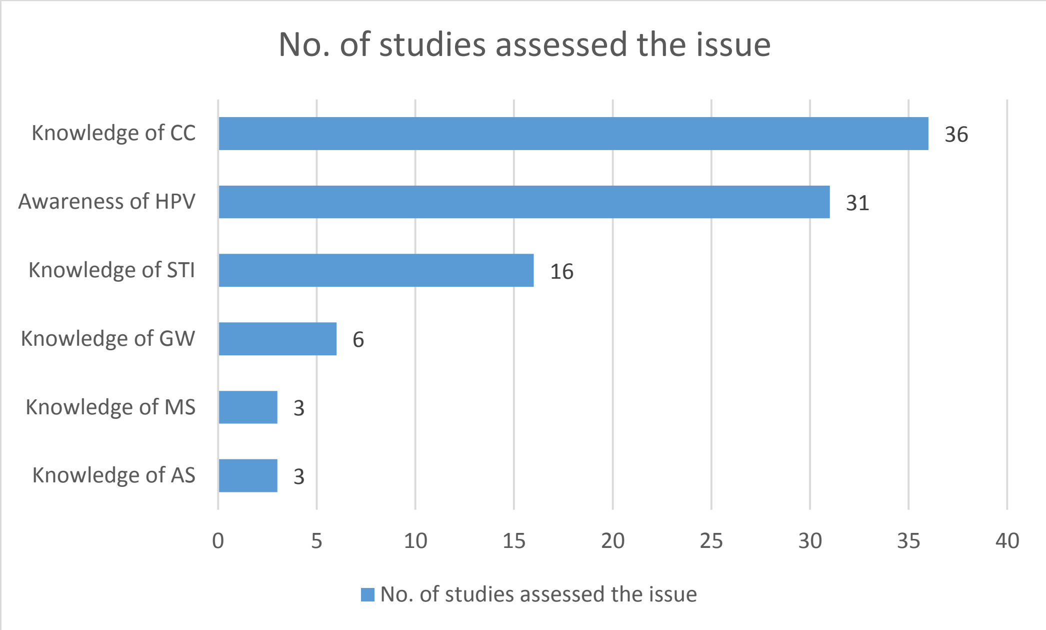


Figure 2-8: Distribution of the number of studies in the exploration of knowledge questions



Knowledge of CC: the knowledge of the relationship between HPV and cervical cancer
Awareness of HPV: the awareness of HPV infection
Knowledge of STI: the knowledge of the sexually transmitted nature of HPV infection
Knowledge of GW: the knowledge of the relationship between HPV and genital warts
Knowledge of MS: the knowledge that having multiple sexual partners could increase the risk of being infected with HPV
Knowledge of AS: the knowledge that HPV infection is asymptomatic

Figure 2-9: Distribution of number of studies in the exploration of influencing factors of the acceptability of HPV vaccines

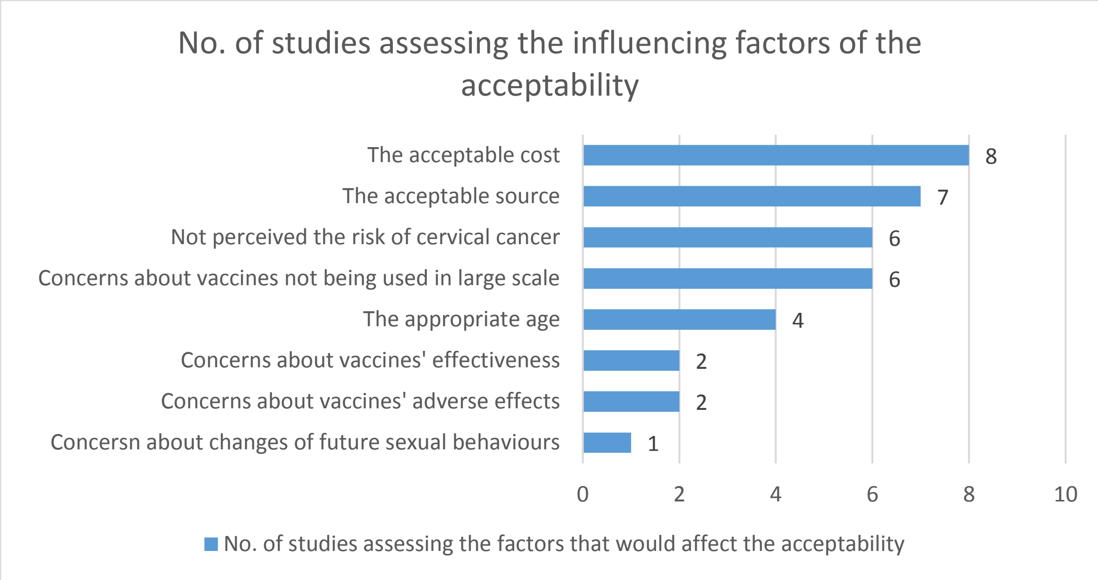


Figure 2-10: Boxplot of results' synthesis: the overview of awareness and knowledge in the different quality of studies

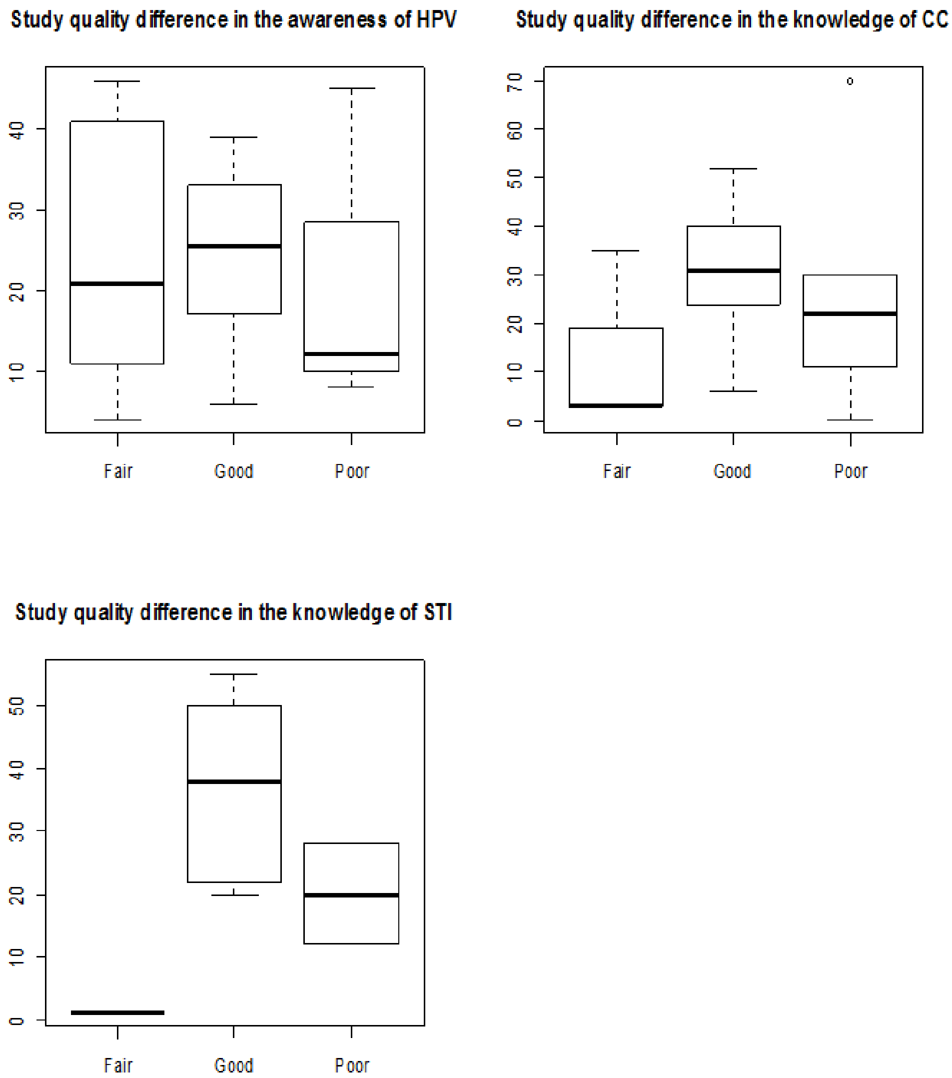


Figure 2-11: Boxplot of results' synthesis: the overview of the awareness and knowledge in different regions

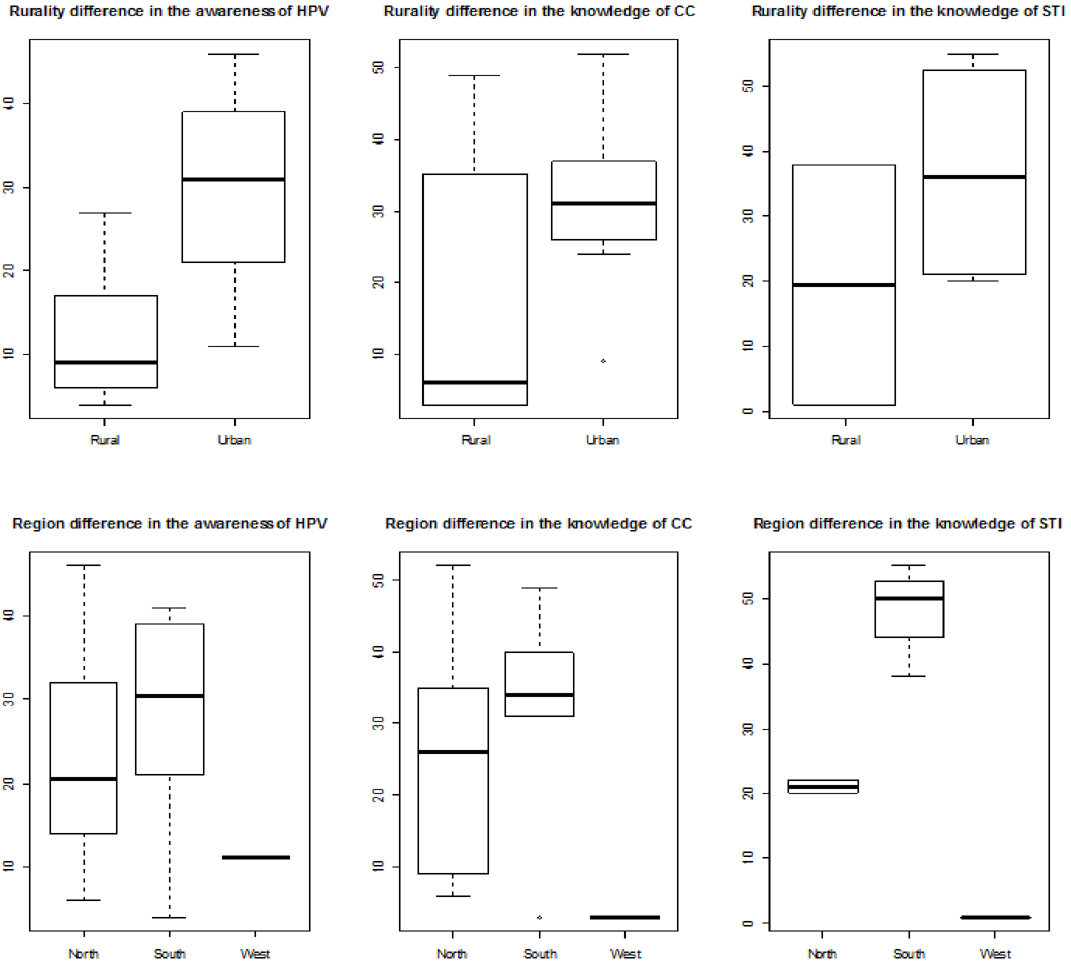
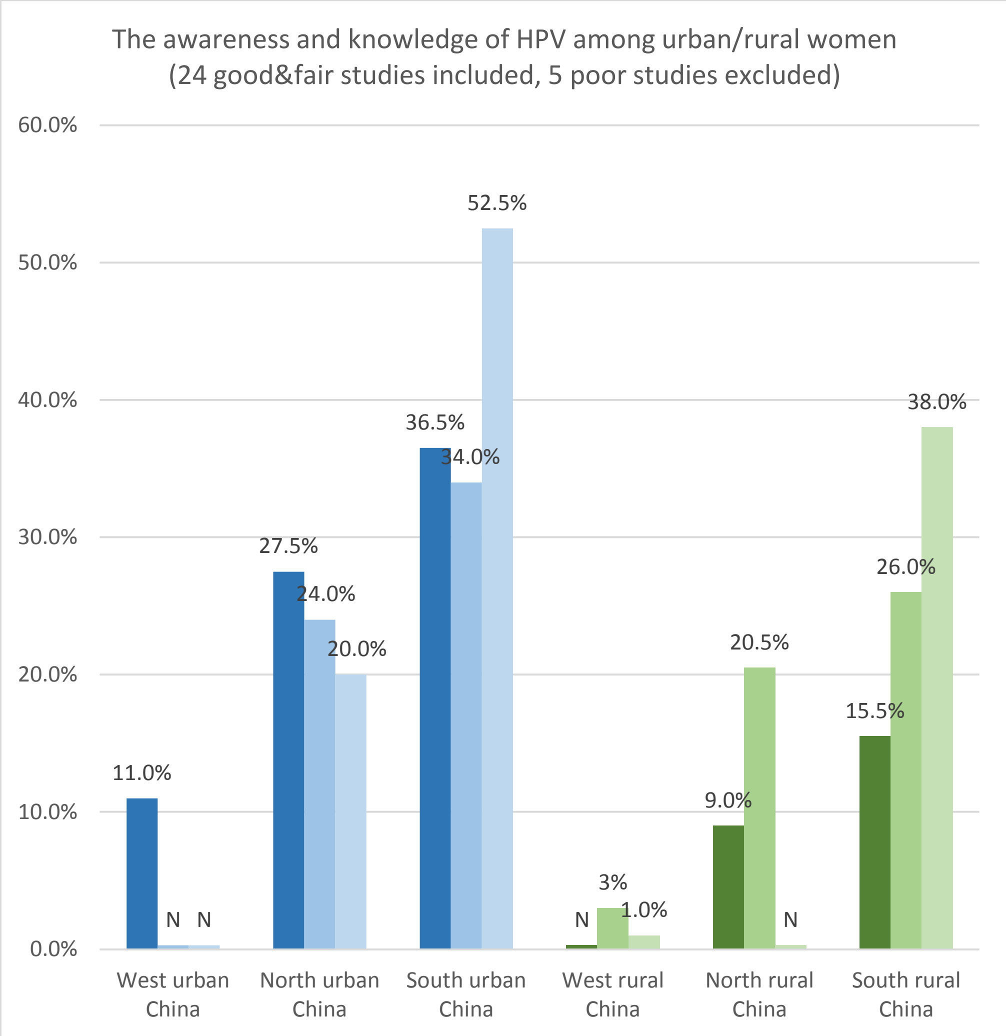
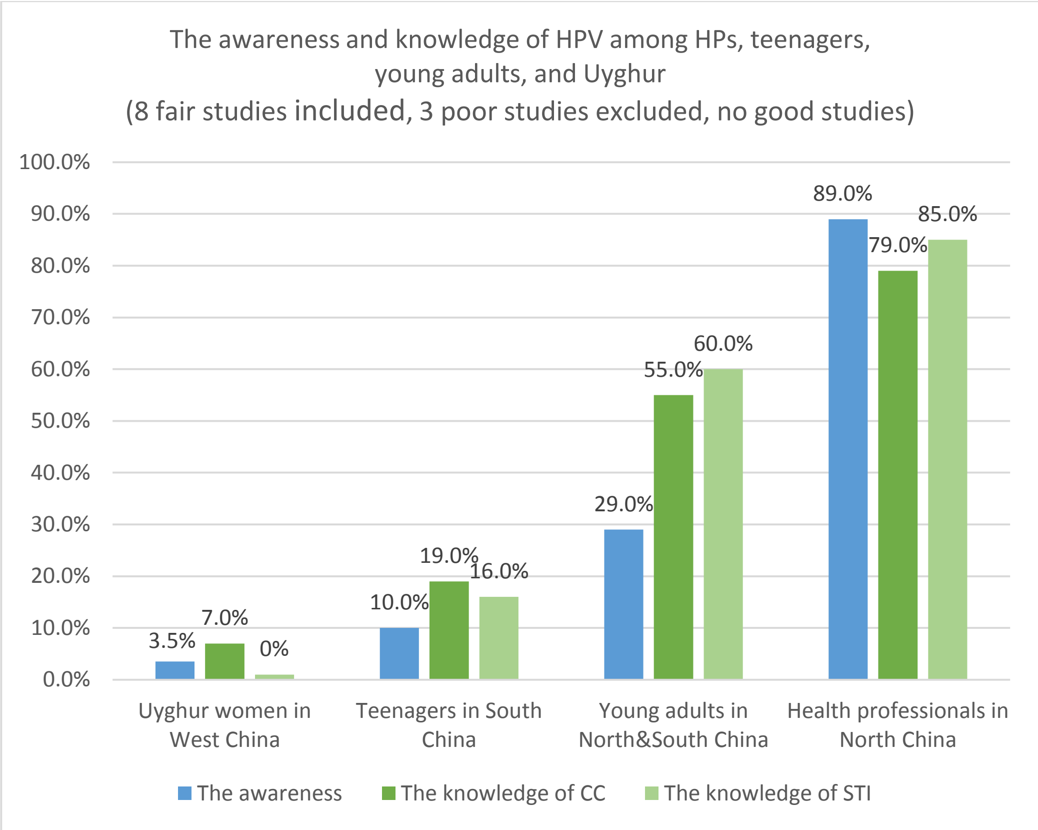


Figure 2-12: The pattern of awareness and knowledge of HPV and vaccination in different regions



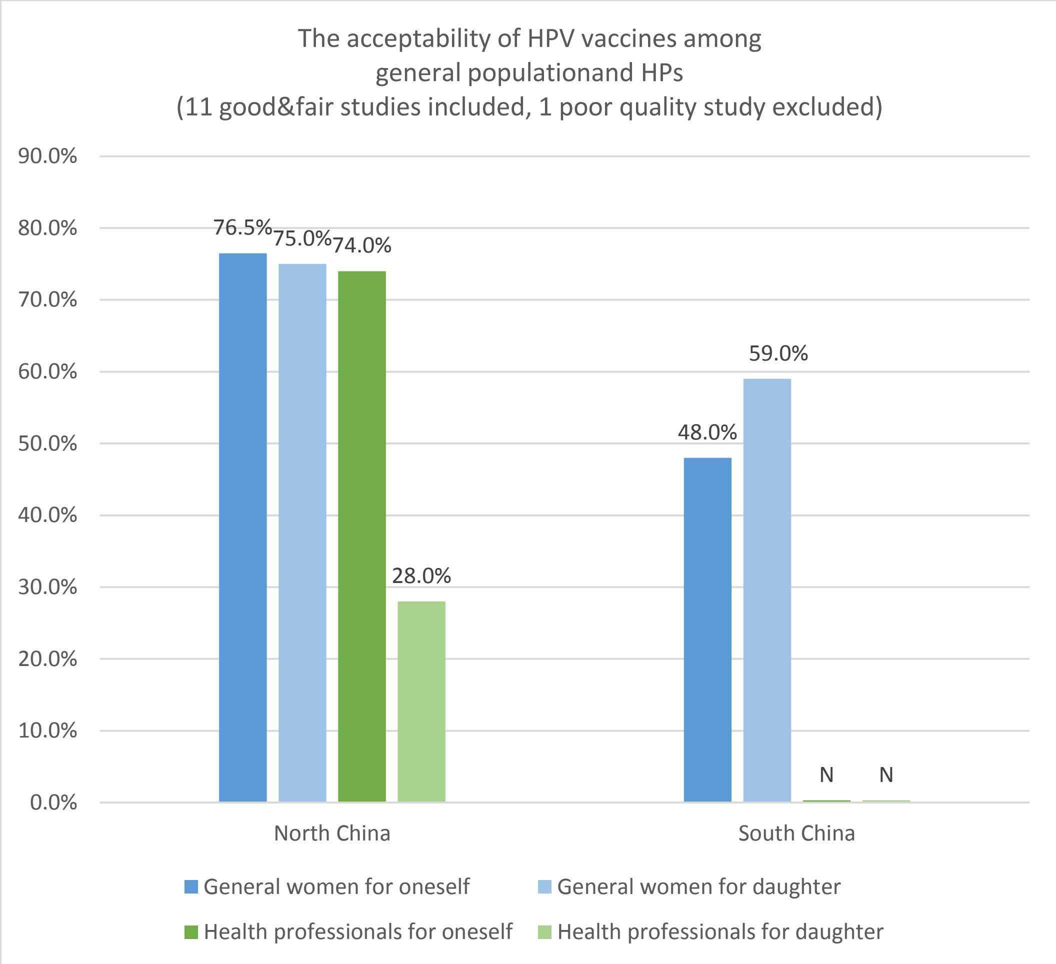
Dark blue/green, medium blue/green, light blue/green mean 'awareness', 'knowledge of CC', and 'knowledge of STI' respectively;
Data is shown by median percentage of studies
Knowledge of CC: Knowledge of the relationship between HPV and cervical cancer
Knowledge of STI: Knowledge of the sexually transmitted nature of HPV
N: no data was reported

Figure 2-13: The pattern of awareness and knowledge of HPV and vaccination among different groups of participants



Data is shown by median percentage of studies
Knowledge of CC: Knowledge of the relationship between HPV and cervical cancer
Knowledge of SIT: Knowledge of the sexually transmitted nature of HPV

Figure 2-14: The pattern of acceptability of HPV vaccines among the general population and HPs



Data is shown by median percentage of studies
N: no data was reported among health professionals in South China
No data on the acceptability of HPV vaccines was reported in West China
The data on the acceptability of HPV vaccines among health professionals for their daughters (28%) was based on only one study (fair quality) in my review. The validity of the finding is therefore limited and not comparable with other data generated from a greater number of studies.

3 Chapter 3 HPV and cervical screening survey: Background and methods

In this chapter I describe the questionnaire survey I undertook in China in 2013. First, I present a brief overview of the 3 key components of my survey, and associated timings:

1. Preparatory work: this was undertaken in Edinburgh (August, 2012-January, 2013)

- I chose a sample, determined the sample size and the mode of survey distribution
- I developed a questionnaire suitable for my survey and the potential participants
- I refined the instrument by conducting cognitive interviews among Chinese students in Edinburgh
- I obtained ethical approval from the University of Edinburgh

2. Data collection: this was undertaken in Heilongjiang, China (March, 2013-May, 2013)

- I travelled to China and conducted the survey in Mudanjiang city, Heilongjiang province between end of March and end of May in 2013
- I obtained ethical approval in Mudanjiang Medical University.
- I recruited schools, grades, classes and students in 5 high schools
- I distributed questionnaires and collected them from participants in class. I supervised the whole process

3. Data management and analysis: this was undertaken in Edinburgh (June, 2013-Dec, 2013)

- I sent back questionnaires to Edinburgh
- I undertook data coding, entry and analysis.

3.1 Background

The objective of my thesis is to explore knowledge of and attitudes towards HPV vaccines among Chinese teenagers. My systematic review of Chinese literature has identified relevant issues in China among a wide range of people; a few studies from the English literature have also examined issues in China, but the perceptions of teenagers have not been examined thoroughly. Moreover, existing studies in the Chinese literature are mostly hindered by poorly described methods – particularly in terms of instrument development, recruitment, and sampling processes; this may compromise the validity of the findings. Hence, I intended to carry out a study based on a robust methodology among high school students, aiming to provide a clearer picture of HPV vaccine knowledge and attitudes amongst Chinese teenagers.

3.1.1 Overview of HPV vaccine knowledge and attitudes in China

Findings of my systematic review of Chinese literature

My review showed that variation in study location and the diversity of participants' demographics are associated with different levels of awareness of HPV infection. For example, adult Uyghur women and rural adult women and teenagers had a low level (<10%) of awareness of HPV. Young adults and urban women adults had a moderate level (approximately 30%), and health professionals had a high level of awareness (>85%). A similar pattern (rural adult women knew least while health professionals knew most) was also found in the knowledge of the relationship between HPV and cervical cancer, and of the sexually transmitted nature of HPV—the two most examined areas of knowledge in my systematic review (Chapter 2 presents the findings).

The level of acceptability of HPV vaccination varied from 28% to 77% - influenced mainly by levels of knowledge. For example, if HPV vaccination is targeted to oneself, acceptability is high, but if the target is one's daughter, acceptability is low. The factors most commonly explored which can influence acceptability are the vaccine's cost, the venue at which it would be offered, and the age at which it would be given.

Review of the English literature studies conducted in China

A small number of studies in the English literature have examined HPV vaccine knowledge and attitudes in China, survey participants in these studies were mostly female adults (including parents of adolescents) [123, 124, 201] and young adults (college students) [128, 129]. Awareness of HPV differed from a low, moderate level to a high level, depending on age of respondents and date of study [123, 124, 128, 129, 201]. The acceptability of HPV vaccines varied from a moderate to a high level, influenced by the population sub-groups (eg. female adults or young adults). No clear pattern has been observed due to the limited existing data in the English literature [123, 124, 128, 129, 201].

The gaps in evidence and methodology I want to address

The findings of my systematic review and studies in the English literature carried out in China highlighted the need for further work in this area. Below are the gaps in evidence and methodology weaknesses in existing studies which I want to address in my survey:

- Content: very few studies examined issues of acceptability and attitudes among Chinese teenager populations; some issues identified in western literature were largely absent from Chinese literature, for example:

    - ‘Do people know there is a need for continued Pap screening after vaccination?’
    - ‘Would attitudes surrounding the perceived benefits of HPV vaccination affect its acceptability?’
- Quality: The instruments used in studies carried out in China are typically not evidence- and theory-based; methods of recruitment and sampling are not well described, and the interpretation of results typically lacks assessments of confounding and potential bias.

Hence I decided to develop a methodologically robust questionnaire-based survey to address these gaps in knowledge.

3.1.2 Methods commonly used in Chinese studies on these topics

Commonly used methods of studies in China

In western literature, multi-centre population-based studies were the most common (over three quarters of studies) [123, 124, 128, 129, 201], and in my review hospital-based studies were the main mode of survey in these studies (approximately 60%). College/school-based studies did not feature prominently in China, in both English and Chinese published literature. With respect to study instruments, only one study in my review used telephone interviews - the remainder used questionnaire surveys, either interview-administrated (23%) or self-administrated. Cluster and random sampling methods were mostly reported in both English and Chinese literature [123, 124, 128, 129, 201], but insufficient descriptions of key methodological elements, such as sampling processes, places limitations on the interpretation of findings from these studies.

Background of high school sampling

I considered that a high school-based survey might be the best choice for my survey as my intended participants are school-age young people. But the variety of types of high school in China makes it difficult to choose, in a rigorous way, a representative sample of high-school students. Hence I intended to choose a sample that would be representative of the majority of them.

There are public and private high schools in China. Private high schools are viewed as informal, and they have a completely different education system, preparing students to attend Western universities. The majority of Chinese students attend public high schools and choose to go to Chinese universities. My intention was to undertake sampling in public high schools. Middle school graduates are allowed to attend a range of public high schools, which are divided into the following categories

- Ordinary independent high school
- Key independent high school
- Vocational high school
- Combined middle and high school
- Minority high school

The categories may vary between individual provinces – for example, in Heilongjiang province, the minority high school is a Korean ethnic high school. The education system is generally the same in all the categories of high schools. Apart from vocational high schools, all high school graduates are required to sit a national college entrance exam prior to attending university. Korean ethnic high school graduates have different subjects in the exam.

Public high schools recruit students based on their academic ranking in the high school entrance exam. In Heilongjiang, approximately the top 60–75% of middle school graduates go to public independent high schools, and the remaining students go to vocational schools or stop school and look for jobs. Hence, students at vocational schools may have the lowest academic performance and records.

Difficulty in obtaining data on sexual behaviours

One of the factors affecting HPV infection and cervical cancer is sexual behaviours (eg age of sexual debut, number of partners, condom use etc), and I wanted to include questions on this topic in my survey. But considering of the difficulty in obtaining valid information in these areas in China, I omitted questions on these topics. Difficulties include:

- Findings of self-reported sexual behaviour might be undermined by the accuracy of self-reporting among school-age young people
- Findings from parents' reports of their children's sexual behaviour might be underestimated
- Chinese culture and societal customs do not encourage discussing sexual issues with others (eg friends, parents).

A few western literature studies have reported sexual behaviours in China, but still the data might be underestimated due to the cultural factors and social norms. Three multi-centre studies (3–28 provincial units) carried out between 2005 and 2008 in China [202-204] have explored factors relating to sexual behaviours amongst high school and college students (12,313–224,770 students). The main findings include the prevalence of sexual activity (4.5–5.9% of high school students [202-204], 11.3% of college students [202]), the unintended pregnancy rate (24.2% of college students) [202], and the prevalence of condom use (49.7% in college students[202]; 11.9% of high school students [204] reported consistent condom use). Nevertheless, because of the lack of methodological detail in the studies and lack of updated information for the years after 2008, it is difficult to make comparisons with studies based on young people in other Asian countries and Western countries.

3.2 Aims and objectives

The objective was to develop and implement a population-based survey which explored knowledge of and attitudes towards HPV infection and vaccines amongst teenagers in China. Specifically, the survey addressed the following questions:

1. What is the level of knowledge of, acceptability of, and attitudes towards HPV and vaccination among school-age young people in Heilongjiang?
2. How do demographics affect knowledge of, acceptability of, and attitudes towards HPV?
3. What are the predictors for the acceptability of HPV vaccination and how do they act as predictors?

3.3 Choice of methodological approach for my survey

Based on the objectives of my survey and my review of the literature, I chose to undertake a school-based, self-administrated questionnaire survey in Heilongjiang province. Considerations are presented later in this section. Figure 3-1 provides a graphical representation of key elements of my survey.

3.3.1 Generating a representative sample

China has 31 provincial regions. The diversity in geography, demography, economy, and education makes it difficult to choose a sample which is representative of the whole country. A one-province study must be less generalisable than multi-centre studies in China, but given my available academic network and budgets, I decided to choose Heilongjiang province as my survey location. The study was conducted in one middle-income city (Mudanjiang city in Heilongjiang province) and two small counties (Ning’an county and Hailin county in Heilongjiang province). The characteristics and representativeness of the study region are described later in this chapter.

3.3.2 Mode of survey distribution and data collection

In deciding upon the best approach to this survey, a number of design issues and methodological approaches were taken into account - bearing in mind the unique social, cultural, and organisational factors that prevail in China.

Table 3-1 summarises a number of modes of administration of the questionnaire and the pros and cons of each approach based on the prevailing local context in China. While a large postal questionnaire survey might have been desirable in terms of numbers of responses, there are logistical issues in conducting such studies in China, particularly relating to the use of the postal system by the Chinese population. The most desirable option thus seemed to be one in which I accessed populations through health and educational institutions. As indicated in the table, these kinds of approaches, in which sampling might be considered to be based on a 'convenience sample', have their own set of limitations; my principal concern is sampling bias (which I will address later in this chapter).

Ultimately I decided on a school-based survey - I considered this to be feasible, given my available time and resources, and I considered school-based samples to have significant potential to provide results that are representative of the wider population. While recognising the caution required in using school-based sampling approaches, the reasons for choosing this method were:

- it is logistically very difficult to conduct postal surveys in China
- schools offer an accessible sampling frame with students from a broad cross-section of Chinese society
- my existing connections with regional health and educational networks facilitated my access to schools for the purposes of conducting surveys
- many existing surveys on HPV vaccination in the international literature have been undertaken in schools, increasing the potential for international comparisons.

3.4 Development of the questionnaire

I developed a self-administered questionnaire by reviewing both Chinese and international literature. I adopted a few steps to develop my questionnaire. First, I decided what the structure of the questionnaire and the response format would be. Second, I formulated the questions based on the theory I had chosen from my literature review. Finally, I performed a cognitive review process to refine the draft questions. Figure 3-2 presents the key elements of my questionnaire development process. The questionnaire is in Appendices 4 and 5.

3.4.1 Structure of questionnaire

I based the development of the questionnaire on the objective of my survey and my literature review of international and Chinese studies. Two main topical issues (knowledge and attitudes) were of interest to me, and hence, the survey instrument comprises 3 sections:

- Section 1: knowledge of HPV infection and vaccines
- Section 2: attitudes towards HPV infection and vaccines
- Section 3: background characteristics

The broad range of areas of enquiry in the questionnaire meant that different response types were needed for different questions. For example, knowledge questions required a 'categorical' true/false/don't know response, while attitudinal questions required scoring on a 5-point Likert scale (with, for example, responses ranging from strongly disagree to strongly agree).

A rudimentary level of knowledge about HPV infection and vaccination was required to complete the knowledge section of questionnaire. There would be little point in asking detailed knowledge questions in areas where there was no basic understanding of the topic. Therefore, the questionnaire started with a 'screening' knowledge question, asking participants if they have ever heard of the HPV. If not, they were instructed to skip over the remainder of the knowledge questions. Nevertheless, I still considered, after some deliberation, that it was reasonable to collect data on attitudes towards vaccination amongst those who indicated no knowledge of HPV infection.

In order to assist participants whose knowledge of HPV infection and vaccination may be limited and who would otherwise find it difficult to answer attitudinal questions, an information box with key facts about HPV and vaccination was provided before the attitude questions were asked. Information was provided in areas including risk factors for HPV infection, the transmission mode of HPV infection, the target population, and the transient nature of HPV infection. Of course, the information box would have helped respondents complete the knowledge questions in Section 1, so I needed to take steps to prevent participants from changing answers after reading the information box. A sentence was put in front of the information box stating 'Please do NOT change your answers in Section 1 after reading the information box.' Further, this point was emphasised in front of the class after the questionnaires were distributed by stating: 'We value your honest answers rather than the correct ones - please don't change your answers once you've read the information in the knowledge box.' Splitting the questionnaire and distributing the knowledge and attitude sections separately was also considered, but, this would have been logistically difficult and may have compromised the distribution process and the rate of return.

3.4.2 Sources of questions

Items in the questionnaires were drawn from a number of sources, including studies in the previous review of western [121, 122, 205-207] and Chinese literature [123, 124, 187, 201] (some of which provided sample survey instruments). Details are described below.

Section 1: Knowledge

The main questions concerning knowledge were generated by reviewing several relevant studies conducted in Italy [206], the US [207], Germany [205], Korea [198], and Hong Kong [187, 208, 209]. These areas of knowledge included:

- risk factors in HPV infection
- protective factors in HPV infection
- symptoms of HPV infection
- the most suitable people to receive HPV vaccination

The wording of the questions extracted from the literature (and the order in which they were presented) was modified to make them more appropriate for a survey of teenagers.

Through consideration of the characteristics of the target population (young teenagers, who tended to have less health knowledge) and the setting (Heilongjiang province of China, where HPV vaccines have not been introduced and cervical screening has not been carried out extensively) some of the questions were excluded, such as knowledge of the HPV DNA test, HPV treatment, and HPV health consequences. Further, I aimed to explore basic knowledge and understanding of concepts relating to HPV rather than more technical aspects and medical knowledge of HPV among my sample; in-depth knowledge questions (eg 'Pap smear' is more technical than 'cervical screening' for teenagers) were also excluded.

Section 2: Attitudes

To formulate attitude questions, I found, in international literature, a number of health behaviour theories that could guide the development of my questionnaire. Below are the chosen theories that influenced the development of my attitudes questions.

Health behaviour theories

Numerous health behaviour theories have been developed since the 1950s [210-214]. Theories are used to guide practitioners to understanding behaviour change in a systematic way and provide evidence for further health interventions. By reviewing literature [210-212], I found five health behaviour theories that are currently widely used:

- Health Belief Model (HBM) [210-212]
- Theory of Reasoned Action (TRA) [210-212]
- Theory of Planned Behavior (TPB) [210-212]
- Social Cognitive Theory (SCT) [210-212, 215]
- Transtheoretical Model (TTM) [210-212]

The theories can be categorised based on individual, interpersonal, and community levels [210] or theory purpose – there are both explanatory theories and change theories [210, 211]. As the level name implies, individual-level theories (eg HBM, TTM) are used to help people adopt healthy behaviours or eliminate unhealthy behaviours [210]; interpersonal theories (eg TRA, SCT) focus on support and control [210]; community theories (eg ecological approaches) mostly offer information to promote community-level behaviour change and guide community interventions [210]. As the purpose indicates, explanatory theories (eg HBM, TRB, SCT) provide an explanation for why people have certain behaviours, and change theories (eg TTM) help to find what factors will influence future intervention programmes (and how).

To identify the most appropriate theory for my survey, I looked at each theory's key elements and constructs. Noar 2005 [212, 214] reviewed the similarities and differences of the elements of the five theories. The similar elements were the general ones for predicting health behaviour: positive/negative aspects of the behaviour, other people's support, one's ability to perform the behaviour, one's risk if not engaged in the behaviour (Table 3-2 presents the details of each theory). And the different elements of theories related mostly to their application to different scenarios [212-217]. A summary of the application of these theories is described below, and a comparison of these theories is listed in Table 3-2.

- HBM mostly applies to assessing illness avoidance and asymptomatic prevention-based health concerns (eg cancer screening, injury prevention) [212];
- TRA/TPB mostly applies to more rational behaviours and those that have a potentially strong intention-behaviour link (eg addictive behaviours: tobacco use) [213];

- SCT mostly applies to reciprocal relationships between individuals and their environment (eg eating habits, contraception) [215];
- TTM mostly applies to deliberate behaviours (eg drug use, weight management) [216, 217].

Hence, factors such as whether one has strong intentions or commitment, or even plans to engage in the behaviour are not included in HBM compared with other theories – but these factors were not my key concern. In terms of theory level, purpose, and applied scenarios, the theory of HBM appeared most appropriate to develop the attitudinal section of my instrument.

HBM constructs

Many of the attitudinal questions were drawn from the concepts of the HBM [198, 199]. There are five such concepts, described below. Nevertheless, some areas of attitude were not covered (eg stigma). Hence, questions on the stigma of HPV infection were generated from the literature review [187, 199, 208, 209, 218]; again, relevant changes were made to the wording, order, and phrasing of the questions. These concepts were adapted as follows:

- Perceived susceptibility/risk (eg 'how likely is it you will be infected with HPV in the future?')
- Perceived severity (eg 'do you agree that HPV infection will have a serious impact on your physical health?')
- Perceived effectiveness/benefits (eg 'do you agree that the vaccine may help you avoid cervical cancer?')
- Perceived barriers (eg 'do you agree or disagree with the statement "I am concerned that HPV vaccines may have major side effects such as long term illness')
- Cues to action (eg 'I would get vaccinated if doctors or nurses recommend me to do so').

Regarding HPV-related stigma, questions such as 'Do you agree people will think someone who is infected with HPV is likely to have been promiscuous?' were included in my survey instrument. Details of the questionnaire are in Appendices 4 and 5.

Section 3: Background

The third section of the questionnaire comprised background data: age, gender, rurality, high school, and self-reported lifestyle behaviours. The lifestyle question concerned smoking behaviour. The reason for this is that I assumed that teenagers who engaged in high risk health behaviours would have different attitudes towards HPV, and smoking acted as a proxy for this. So I was interested in whether smoking behaviour was associated with teenagers' knowledge and attitudes towards HPV and vaccines.

3.4.3 Refinement of draft questions: Cognitive interviews

The process of cognitive interviewing is an important technique in refining draft questionnaires, testing their capacity to be understood and eliciting valid responses in the chosen target population [219].

Approaches to the cognitive interview

From interview goal perspectives, cognitive interview can be categorised into three types [219]:

- concept elicitation,
- cognitive debriefing (which I chose to use in my cognitive interviews)
- a combined elicitation/debriefing interview.

Concept elicitation interviews are generally used to identify constructs generated from participants' perception and provide evidence of the validity of the instrument. Cognitive debriefing interviews are used for the development and modification of the questionnaire to reduce measurement error – I chose this approach for my cognitive interview, based on the interview objectives (to obtain the most accurate, or valid, responses).

Various techniques are employed in conducting cognitive interviews [219]. They include (but are not restricted to):

- think-aloud interviewing (used in my interview)
- verbal probing techniques
- concurrent verbal probing (used in my interview)
- retrospective verbal probing.

Based on my available resources and interview scenarios, I chose concurrent probing and think-aloud interviewing techniques for my interviews. This meant that participants were required to read the questions in the questionnaire and verbalise their thinking process during the interview. Issues raised by this method include:

- The wording of the questions: either difficult to understand or interpretations vary among different participants

- The response selection (categories): either mutually exclusive or social desirability bias.
- The reference period for information recall: either too long or too short.

Conduct of the cognitive interview

While it was not feasible to undertake interviews among teenage high school students living in China, I considered Edinburgh-based Chinese students to be a reasonable proxy; they were only marginally older than my survey participants, and were likely to hold reasonably similar knowledge and attitudes in my key survey domains (although, of course, their exposure to Western culture and the educational environment at Edinburgh would have had some impact). I undertook ten cognitive interviews with 21–24-year-old Chinese students based in Edinburgh. While the age range of interviewees was not ideal for the questionnaire survey, I felt 21–24-year-old Chinese students were young enough to be able to recall from their own experiences what kind of wording and sentence was suitable for high school students. Interviewees were identified through class lists and informal networks, and on each occasion I sat with the respondent at a convenient location while he/she completed the questionnaire and simultaneously offered feedback on whether the questions were clear or difficult to understand.

A number of changes relevant to the wording and structure of the questionnaire were made based on these interviews:

1. Comprehension: There were a couple of instances of misunderstanding of the wording. Since the Chinese translation of HPV involves the word 'nipple', two female respondents mistakenly thought the infection was related to the breast. To minimise confusion between HPV and breast conditions, an explanation of the name HPV was added to the information box before participants answered the attitude questions: 'the word HPV is based on a pathological description, it can cause common warts or genital warts showing papillomatosis, and has nothing to do with the nipple or breast'.

One male student could not differentiate between 'risk factors for cervical cancer' and 'one cause of the cervical cancer' – that is, he felt a little confused about the meaning of the terms 'risk factor' and 'cause'. To address this, the words 'increase/reduce the risk of cervical cancer' were used in the questions instead of terms such as 'risk' or 'protective factor'.

2. Difficulty in remembering or recalling information to provide answers: most of the interviewees thought the question ‘Compared to others of your age, how likely is it you will get HPV infection/cervical cancer in the future?’ was difficult to answer. This was because they needed to consider information relevant to risk or protective factors for HPV infection/cervical cancer in relation to their own behaviours (which some found challenging). Further, most interviewees had limited knowledge of risk and protective factors, and hence they found it difficult to assess their own risk. Some also could not understand the statement ‘HPV infection usually disappears without treatment’.

Based on these responses and the suggestions of interviewees, a number of changes were made, including changes in wording and the provision of more information in the information box - for example, ‘High-risk HPV infection is very common among young men and women, but 70% of infections will be got rid of by the immune system within 1 year’; ‘5–10% of infected women are at risk of developing cervical cancer’; ‘The risk factors for cervical cancer are multiple sexual partners, early pregnancy, multiple pregnancies’, etc. Identification of these extra pieces of information was assisted by a literature review of these topics [220]. Details are presented in the questionnaire (Appendices 4 and 5).

3. Response categories: One male student suggested that friends’ recommendation would be different from parents’, so the question should not combine the two recommendations together into one sentence – so I split the question into two parts.

Two students gave the response ‘unsure’ to the question ‘How likely is it you will get vaccinated?’ – they suggested that not using the neutral option would push participants to think more carefully before choosing the response categories and also avoid participants tending to choose the easiest option unconsciously (which may, indeed, be ‘unsure’). But I wanted know how many people were genuinely unsure or didn’t know about the statement. I found it difficult to respond to this feedback without making this section overly cumbersome. After some deliberation, I simply inserted a sentence at the top of these questions: ‘Please think carefully before answering the following questions.’

3.4.4 Summary

I’ve described, in the preceding paragraphs, the process I undertook in developing the instrument for use in my survey. It is, of course, preferable to use validated instruments for surveys – this leads to greater consistency and comparability of findings between surveys, and gives greater confidence in the validity of survey findings. However, no such instrument existed – my areas of enquiry included knowledge of and attitudes towards cervical cancer and HPV vaccination and the instrument needed to be culturally, and cognitively appropriate for school-age Chinese people; that is, the wording of questions should be tailored to this young group. Survey instruments often need considerable adaptation if they are to be used in different settings and culture. Chinese people may, for example, have relative conservative attitudes towards sex related topics.

Nevertheless, I drew on existing literature wherever possible - I generated the knowledge and attitude questions drawing on the international literature. I generated questions about stigma drawing on studies carried out in Hong Kong where many attitudes and cultural characteristics are similar to those found in mainland China. I also carried out cognitive interviews to refine the questionnaire (all the steps in the development of questionnaire and the measures I have taken were discussed with my supervisors). Hence, I undertook an instrument development process using rigorous questionnaire development techniques – I consider that having a 'bespoke' questionnaire for my survey provided benefits which outweighed the disadvantages of not having a pre-validated instrument.

3.5 Sample size considerations in my survey

This is the stage at which I determined how many participants I should recruit in my survey to achieve the best estimate of the proposed finding on the basis of the available resources and network.

3.5.1 Considerations in the estimation of sample size

Sample size was determined based on the research hypothesis, difference of proportions of the outcome (estimated via prior studies), and the parameter estimates (α: the significance level and β: the statistic power) – that is, the level of precision and certainty I wanted to achieve. Table 3-3 shows all the elements used for sample size estimation, and Table 3-4 shows how these factors affect sample size estimation [221].

Formulae that are used to estimate sample size vary, but there are common general principles. The available formulae comprise of the following parameters [221] (Table 3-3):

- Difference in proportions of the outcome: p_1-p_2
- Statistical power (β) and significance level (α) based on Z scores: Z_β and $Z_{\alpha/2}$

- The ratio of larger group to smaller group: r =1 means the number of males equals to the number of females in my survey.

I used G*Power software (free online: http://www.gpower.hhu.de/) to calculate the sample size by entering the above parameters.

3.5.2 Sample size estimation

Two main research aims determined the sample size calculation: (1) to estimate the level of awareness in the sample with a reasonable level of precision, and (2) to identify associations between a. gender and knowledge, and b. knowledge and acceptability. My calculations indicated the required sample size would be 3,500–4,000 - the justifications for this are below. Figure 3-3 presents the key elements of the estimation.

Estimate of level of awareness

The level of awareness about HPV infection is low amongst Chinese teenagers (around 15% of people know about HPV [131, 155, 222]). With a 95% confidence level (95% probability of the precision of the result) and 80% power (80% probability of finding a significant result), the estimated sample size needed to measure a proportion of 15% of people who know about HPV would be 196. The level of awareness is examined by asking 'Have you ever heard of HPV?', which is also the screening question (used to filter people who were not aware of HPV infection). As I intended to undertake a number of comparisons between variables, a sample size much greater than 196 (around 4,000) was required (see below).

Associations between variables

Hypothesis tests are used to examine associations. The sample size must be large enough to achieve sufficient statistical power to correctly reject the null hypothesis. In questionnaire surveys the usual requirement is to detect a difference in proportions – and to do so with a high level of precision and confidence.

Two central questions needed to be answered in the study; because multiple associations were being examined, there was an increased risk of falsely rejecting the null hypothesis (type I error) - finding a significant result by chance because of the large number of statistical tests taken. Therefore, the *Bonferroni* correction was used to reduce the likelihood of type I errors by only rejecting the null hypothesis for a small p-value (which was 0.05/2=0.025).

1. Gender difference in the level of knowledge was the first comparison. A different measure of level of knowledge was used here compared with the estimate of awareness above. The sample size estimation is described below.

- The research hypothesis: Gender difference existed in knowledge of the association between HPV and cervical cancer (the main measure I used to examine knowledge of HPV).
- Difference of proportions: The gender difference in the knowledge of HPV was 15% (eg 50% males know that HPV causes cervical cancer, and 35% females do not [153]).
- Parameter estimates: The significance level was 2.5%, and the statistical power (a probability of correctly detecting a difference of 15%) was 80%.
- Other factors: Assuming male and female participants were equally distributed in the sample.
- The sample size required would be 412

2. The association between the level of knowledge of HPV and of HPV vaccination was the second comparison. Below is the sample size estimation.

- The hypothesis: The level of knowledge would influence the acceptability of HPV vaccination. Knowledge was measured by asking the question 'Does HPV cause cervical cancer?'
- Difference of proportions: I aimed to detect a 15% acceptability difference (60% vs. 75%) between people who demonstrated knowledge and those who did not [166, 198]. Evidence showed that the level of knowledge of HPV and cervical cancer was around 30% [170, 175].
- The parameter estimates: Assuming the statistical power was 80% to truly detect a 15% acceptability difference and the p value was 0.025.
- Other factors: There were potential confounders to adjust for (i.e. age, gender, and rurality).
- The sample size required would be 500.

However, as I expected that approximately 15% of the population would respond 'yes' to the screening question based on my literature review [131, 155, 222], I needed more than 500 respondents - only those who answered yes got the opportunity to answer the knowledge questions. Hence, it transpired that 2,800–3,500 respondents should be sufficient to produce the required number of people (420–500). Previous similar surveys in China have achieved response rates between 80 and 90% [152, 153]; thus I assumed that questionnaires needed to be provided to a sample of 3,500–4,000.

To summarise, for associations between Section 2 variables (attitudes, beliefs etc) and Section 3 variables (patient characteristics), I used all the respondents' questionnaires. Whereas, for associations between detailed knowledge and other variables, I used approximately 15% of the questionnaires - those from respondents who were aware of HPV.

3.6 Representativeness of my sample (School children in Heilongjiang province)

Selection bias almost always exists in surveys from regions which are small compared to the whole country. Nevertheless, I wanted my findings to be as representative as possible of most adolescents in 'middle-developed' provinces in China. To look at how representative my sample was, I assessed the status of school-age young people in Heilongjiang in the following terms.

The representativeness of Heilongjiang province of the whole country

- Demographics, economic status, education, etc.
- Health care expenditure
- Potential affordability
- Cervical cancer and HPV epidemiology

The representativeness of school-children of all people of the same age in the chosen region

- Demographics
- Academic performances in the chosen region

The data presented later are from *China Statistics Yearbook [149],* and *China Health Statistical Yearbook [223],* which are recognised as a reliable and well-acknowledged health-related databases in China. The data are obtained from multiple levels of government (village, county, township, and provincial), and updated every year by the local government [223]. They have also been used as evidence for the annual central government official report (National Health and Family Planning Commission of China, http://www.nhfpc.gov.cn/).

3.6.1 How representative is Heilongjiang province of the wider Chinese population?

Demography

Heilongjiang province, in the northeast of China, has a population of 38.34 million, and is ranked the 15th most populated province (in the middle) (see Table 3-5 and Figure 3-4) in 22 provinces, 4 municipalities, 5 autonomous regions of China [149, 223]. The proportion of the population that is urban is 55.5%, higher than most provinces of China [149, 223]. There are 53 ethnic groups within the province, and 94.3% of the population is Han, followed by the second and third largest population, of Man and Hui ethnicity respectively [149]. The minority ethnic groups lead a very similar life to the Han population, having no major differences in lifestyle, education, and health conditions (access to health services and health insurance coverage). Thus, Heilongjiang province is viewed as a medium-sized, urbanised province in China.

Economic status of Heilongjiang in China

Gross domestic product (GDP) per capita and household income per capita are the main indicators I used to assess Heilongjiang's economic status in China.

- GDP per capita: ¥32,615, ranked the 16th (in the middle) of 31 provincial regions in China [149, 223] (See Table 3-6, Figure 3-5).
- Average household income per capita: ¥15,696.2 in urban regions, ranked 28th in China; and ¥7,590.7 in rural regions, ranked 10th in China [149, 223]. (Data from other provinces is not shown.)

Hence, Heilongjiang province is viewed as a medium-wealthy province in China and most inner land provinces have roughly similar levels of wealth (8 provincial regions have a similar level of GDP per capita, ¥30,000–40,000; see Table 3-6). The low urban and high rural average household income might indicate the rurality difference of household income is small in Heilongjiang province.

Health care expenditure in China and Heilongjiang province

In China, three components are involved in total health expenditure: Government health expenditure [224], social health expenditure [224], and individual out-of-pocket payment [224]. The average total health expenditure per capita in China was ¥1889 in 2011 [223]. It included

- Government health expenditure (¥554) [223]

- Social health expenditure (¥625) [223]
- Out-of-pocket payment (¥710) [223]

The out-of-pocket payment (health care spending per capita) and its proportion of the total consumption per capita (health consumption proportion) are the two indicators used to assess the affordability of health care for residents. Below are the data for Heilongjiang province.

- Out-of-pocket payment: 978.8 RMB (9th highest in China) in urban residents and 434.3 RMB (5th highest in China) in rural residents [149, 223]. (See Table 3-7)
- The health consumption proportion: 10.2% in urban residents in 2010; 10.2% in rural residents in 2010 [149, 223]. (See Table 3-7).

When the health consumption proportion is over 10%, it indicates a heavy financial burden on households [225]. The health consumption proportion is high in Heilongjiang province in comparison with most other provinces [223] (Figures 3-6 and 3-7), which implies the likely high health financial burden of Heilongjiang residents. Four provincial regions of China (see Table 3-7) had a health consumption proportion of over 10%, which would be comparable to Heilongjiang province.

Demography and economic development of Mudanjiang city

Mudanjiang city is the third largest city in Heilongjiang province, and has emerged as a medium-wealthy and urbanised city (55% are urban residents) in Heilongjiang [226].

Six counties are scattered around the central region of Mudanjiang; Ning'an and Hailin counties are located in the southwest and west of Mudanjiang city, with a population of 440,000 in each (Figures 3-8 and 3-9).

Attendance rate at school

Attendance rates for primary school, middle school, and college in Heilongjiang provinces are generally high—over 95% [223]—but the attendance rate for high school is very low, only 68.1%[223]. Some provincial/municipalities like Beijing and Shanghai have attendance rates of over 100% [223]. No interpretation is available in the statistical yearbook of attendance rates of over 100% or the low attendance rate for high school.

Cervical cancer statistics in Heilongjiang province

No provincial cancer census is available in Heilongjiang province regarding the incidence rate of cervical cancer. A study carried out in Shangzhi county in 2009 reported the crude incidence rate at 15.94/100,000 (ranked 4th among the most common female cancers in the county) [227] and the crude death rate at 3.32/100,000 (ranked the 7th highest death rate of female cancers in the county[227]. Based on the national cancer census in 2004–2005 [17], the standardised death rate for cervical cancer in Heilongjiang province is 2.12/100,000, and the highest death rate is in Xinjiang province (10.69/100,000); the lowest death rate is in Chongqing (1.02/100,000) [11, 17]. (Table 3-8) It was reported that a death rate of 1.5-2.5/100,000 was found in ten provincial regions of China, similar to Heilongjiang province. No geographical pattern was identified in the incidence and mortality rate of cervical cancer.

Variation in economics, ethnic groups, and measurement may contribute to the gap in the death rate and mortality between national census and research-based studies. Death rates are thought to be underestimated by the national cancer census as most cancer registries in China have not established an electronic system, and entirely manual sorting, storage, and organisation may lead to human errors (eg records being defaced, incomplete, or even lost).

Hence, the cervical cancer burden in Heilongjiang might be similar to the other ten provincial regions, but as the upward trend of cervical cancer incidence was observed in the whole country during the last decade (described in Chapter 1), the disease burden might become heavier over the years as well.

HPV prevalence

Difficulties also exist in estimating HPV prevalence in Heilongjiang province (in common with other provincial regions). Provincial regions in China have not set up efficient monitoring systems for HPV infection, though HIV and HBV have been monitored by local Centres for Disease Control (CDC). Data on HPV prevalence can only be obtained from research studies. The same situation prevails in other parts of China, making it difficult to assess the representativeness of HPV prevalence among Heilongjiang residents. Below are the findings from two research-based studies in Heilongjiang province.

A study of 1,759 subjects on HPV prevalence in Daqing city, Heilongjiang [228] reported the positivity of HPV as 8.64% in 2010, while two studies conducted in Harbin hospitals have found higher HPV positivity (21.5%[229] and 31.2%[230]). The difference in HPV positivity may be due to the variation in the selected population. The Daqing study chose women from among government employees, and the Harbin study selected women from among hospital patients.

HPV prevalence might be either underestimated or overestimated in these studies. Hospital patients would have more HPV positivity than ordinary people, but it is difficult to assess the estimates of HPV prevalence among government employees, a distinct group generally with better education and living conditions.

3.6.2 How representative is my sample of school-children?

Senior high schools have been chosen on the basis of both convenience and their potential to provide representative samples. Hence, No. 1, 2, and 3 high schools (schools are typically given numbers to identify them in China), and high schools in Ning'an and Hailin were my sample schools. Details of the selection of schools are given later in this chapter. Here I examine the representativeness of my sample in terms of the students' demographics, academic performances, and their likely family background.

Rurality: No.1, 2, and 3 senior high schools recruit students only from urban regions of Mudanjiang city. Ning'an and Hailin senior high schools recruit students equally from urban and rural regions of the county. The ratio of urban to rural students among the selected schools could influence my results. Based on the estimated enrolment ratio of urban/rural students in the five schools, approximately one fifth of all the participants would have come from rural regions.

Age: I tried to ensure the same proportion of students per age group by selecting an equal number of classes in each grade. These classes were distributed between Grades 10, 11, and 12, with an age range of 15 to 18 years (although a small number of teenagers aged younger than 15 or older than 18 were also included).

Gender**:** The male/female ratio is approximately 1 in these five schools. Involving both girls and boys in the survey was important - it carried the potential to avoid stigmatising females as the source of STIs and improve the social acceptability of HPV vaccine.

Academic performance: Chinese students are required to undertake senior high school entrance exams to attend high school. They are recruited to school based on their academic rankings in the corresponding region (rather than being recruited to the nearest high school). No.1, 2, and 3 senior high schools recruited the top 60.2% of students in the central regions of Mudanjiang city; students in Ning'an senior high school are in the top 74.3% of Ning'an county; and Hailin senior high school recruits the top 66.7% of students in Hailin county. These data comes from a local government report in 2013 [231]. Hence, the results from the five chosen schools could not be generalised to all teenagers at high schools, but 'good students' of the target region in Heilongjiang province.

<u>Family background:</u> High school students in my survey come from diverse family backgrounds. Because the selected schools were all public high schools recruiting students based on the entrance exam, there should not be significant over-representation of any specific social class. Ideally, access to high school education is almost equal to all the students regardless of their backgrounds. Nevertheless, those who achieve better academic records are usually from relatively wealthy families or highly educated families. Hence, my sample of students would be more likely to have wealthy and well-educated parents.

Some students in Chinese high schools have financial problems due to family circumstances. For students who are unable to pay tuition fees, state-funded programmes help to subsidise them, covering all their tuition fees and some part of their living expenses. The proportion of funded students is 20% in each public high school in Mudanjiang city, including affiliated counties (again, this is fairly consistent with other regions of China). Due to the difficulty in obtaining information about family income from high school students (it is sensitive, and/or they may be too young to know the details), I did not request this information in the questionnaire. Parents' background may, of course, play an influential role in students' perspectives when acquiring knowledge related to sex, but it was not my primary research question in the survey.

3.6.3 Conclusion

I have attempted, in this section, to assess how representative my sample is – by examining both the characteristics of Heilongjiang province, and of my school-based sample. I've examined factors including demography, economy, education, and health care. Based on the China Statistical Yearbook (summarised in Table 3-9), Heilongjiang is viewed as being in the top third of urbanised provinces in China, with a middle-size population. Five central provinces (Hebei, Shaanxi, Hunan, Shanxi, Liaoning) share a similar index (in terms of economy and health care expenditure) to Heilongjiang (Figures 3-4, 3-5, 3-6 and 3-7). It is not an especially wealthy province (ranked in the second half) but has higher health expenditure than average, and residents, on average, spend more out-of-pocket money than two-thirds of Chinese people for their health, irrespective of whether they are urban or rural. It may be inferred from this that Heilongjiang residents would be more likely to experience financial burden related to health than most of other provinces (around two thirds) in China.

The potential selection bias of the students in my survey relates to their greater likelihood of having a higher level of academic performance, and parents from wealthier, better-educated backgrounds. I will discuss these issues further in the next chapter.

3.7 My recruitment process

I decided on a school-based survey in Mudanjiang city of Heilongjiang and chose my sample at multiple levels, starting from schools to grades, classes, and students. The recruitment process is presented in Figure 3-1.

3.7.1 Selection of schools and eligible criteria

Due to the variety of high school systems in China, I established inclusion and exclusion criteria for the selection of the schools. The inclusion criteria were:

- public high schools
- schools with Grades 10, 11, and 12

The exclusion criteria were:

- ethnic minority high schools (in Mudanjiang city, this refers to the Korean ethnic high school)
- vocational high schools (to prepare students for specific jobs)
- private high schools
- international high schools

The chosen schools were:

- Numbers 1, 2, and 3 senior high schools in Mudanjiang city
- Ning’an senior high school in Ning’an county of Mudanjiang city
- Hailin senior high school in Hailin county of Mudanjiang city

3.7.2 Selection of grades, classes, and students

Within the five high schools, students were randomly allocated to different classes based on their student identity number (student ID) when they started school at Grade 10. The selection method for classes reflects both convenience and representativeness. I selected 13 or 14 classes in each school, and four or five classes from each grade. The average number per class is around 60.

In Grade 10, four or five classes in each school were chosen by convenience (depending on whether teachers were available at my first visit). In Grades 11 and 12 of all the high schools, classes are categorised into two types: science and arts. The ratio of science classes to arts classes of all the selected schools is approximately 2:1. I chose one or two arts classes and two or three science classes in Grades 11 and 12 of each school. Therefore, more science students were included in the survey than arts students. Differences may exist in terms of knowledge of HPV between science and arts students, but considering the difficulty in logistics and the priority of my research questions, I did not collect information on the class type (no questions were asked in the questionnaire about the class categories).

I decided to distribute around 780–850 questionnaires in each school, based on my sample size calculations. The students were those from classes whose teachers had given their prior approval before conducting the survey. During the negotiation process with each class, a teacher of one class in Grade 12 from No. 1 high school rejected my request to let her students participate in the survey because students in the class had very busy schedules, so no survey was conducted in this class. No other students asked for leave from the classroom before the survey started. Questionnaires were given to all the students sitting in the classrooms of the chosen classes. Students who declined to participate after they had read the questionnaire did not return their questionnaire. No relevant information was obtained from them. For privacy and ethical reasons, I did not ask who the non-responders were in the class.

3.8 My survey administration process

Official approval was obtained from the Educational Departments in Mudanjiang city to carry out the questionnaire survey in the five high schools. Ethical approval was obtained from the ethics committee of Mudanjiang Medical University (Appendix 6, the Chinese document of ethical approval).

The survey took me two months to administer (from end of March to end of May 2013), including three visits in each school (see Table 3-10).

I visited each school three times to conduct the survey.

Visit 1: 20 March–5April. I contacted the headmaster of each school by telephone and gained approval. I visited each school and talked to the director of each grade about the project. These directors helped me to confirm the teachers of the selected classes. Then when teachers were available, I talked to them about the study and arranged a mutually agreeable time (a period of self-study rather than a didactic teaching lesson) to speak to the whole class about the survey. On average, I took two days to talk to the teachers, arranging the time to visit each school. All but a teacher of Grade 12 in No. 1 high school agreed to let their students participate in the survey.

Visits 2 & 3: Visits 2 and Visit 3 were conducted close together in each school (within two weeks). Only once I had finished the survey in one school did I start the survey in another school (the timeline of visits to each school is presented in Table 3-10). In each school, I came to each class accompanied by the class teacher, explaining why and how the study would be carried out and to clarify some common areas of confusion around HPV infection - such as the difference between HPV and HIV. Care was taken to limit the amount of direct information given about HPV, as this could have influenced the participants' responses.

I spent about 5 minutes speaking with each class. During this time I covered the following points:

- I introduced myself, typically along the lines of: '*thanks for giving me the opportunity to speak with you. I'm originally from Mudanjiang city; I am now a PhD student at the University of Edinburgh in the UK, working in the area of public health. I am carrying out a questionnaire survey to learn more what young people like you know and think about the introduction of HPV vaccination'*
- Summarised key points from the information sheet (eg clarified that the survey was about HPV, not HIV/AIDS)
- Gave out the invitation letter and information sheets (Appendices 7, 8, 9 and 10), assured students that if they took part in the survey, their responses would be confidential
- Encouraged them to read these documents before my next visit (and told them the time of Visit 3)
- Told them they could discuss this with their parents if they wished
- Told the class that in the final phase of my PhD (one year and a half later), I would send a project summary and copies of academic papers to the head teacher so that they would know the results of the survey.

Students were given two or three days to consider the study and decide whether they would take part in the survey. The exact time for the third visit depended on their curriculum of each class over two or three days. Except for Grade 12, students of Grades 10 and 11 had a self-study class every afternoon in all the chosen schools. In terms of Grade 12, Ning'an and Hailin high schools arranged self-study classes every evening from 7pm to 9pm; and students in No. 1, 2, 3 high schools had one self-study class every afternoon or every other day. I had confirmed the third visit time with the teachers during the second visit and let the students know. In Visit 2, when students had further queries about the survey, I provided information to them on that day, or else they were able to contact me directly afterwards. My contact details were given on the information sheet. I did not receive any emails or phone calls from students or their parents about the survey.

Visit 3: I visited the included classes at the agreed date and time (Table 3-10). I identified those students who had decided to take part in the survey. No students indicated that they would not participate in the survey. They all wanted to read the questionnaires before their final decision. Then the participants were given the questionnaire and asked to complete it by themselves: I emphasised a number of points with approximately the following wording:

- *'First, we value your honest answers rather than correct ones, so please answer the questions honestly no matter how little or how much knowledge you have.*
- *Second, do not turn to the next page until you finish the first page. Once you read the HPV information in Section 2, please do not change your answers in Section 1.*
- *Third, please complete the questionnaire by yourself and do not look at other's responses or chat with other students: please respect the privacy of your classmates*
- *Fourth, HPV is not the same as HIV/AIDS, please do not get confused.*
- *Fifth, students who live in the following places constitute urban residents: four districts of Mudanjiang city, Ning'an and Hailin county; students who live in the following places constitute rural residents: townships and villages in Mudanjiang, Ning'an, and Hailin'*

I stayed in the classroom waiting for the students to complete the questionnaire and was therefore available to respond to any queries. I talked to the teachers and hoped that they would not be present in the classroom during the survey (I was concerned this might influence the validity of student responses). Most of the teachers agreed and left the classroom, while a small number of teachers stood in front of the classroom for a while and then left. No teacher observed the whole process of the survey. I observed the students and encouraged them to complete the survey in silence. Students were asked to put the completed questionnaires into a collection box at the front of the class.

The students' participation was not confidential because students who took part in the survey were known by their teacher and the other students in the same class; there was no obvious way of avoiding this. Nevertheless the answers in the questionnaire were and will be kept strictly confidential. Students who declined to participate were not known by others. The classroom was spacious and every student had their own desk, seated in different lines and rows. Participants could not easily see the responses of other participants who were seated in a separate row. The questionnaire was anonymous - no identifying information was included. The completed questionnaires were stored initially in secure filing cabinets in offices at Mudanjiang Medical University, then transported back to the UK for secure storage at the University of Edinburgh.

A number of further measures were undertaken to enhance the integrity of the questionnaire-completion process and the validity of responses. These included measures to ensure the questionnaire was completed in private, protection of confidentiality, and clarification over the confusion between HPV and HIV, etc. For quality control purposes, I did not check for missing or invalid responses at Visit 3. In the data entry process using Epidata software, missing data were not recorded as any number, just left blank; but SPSS (the statistical software used for data analysis), included missing data in the descriptive analysis – these data were excluded from further comparisons. So the amount of missing data was known but was not analysed included a as variable.

3.9 Data management

3.9.1 Transport and storage of questionnaires

Before visiting the high schools and after gaining ethical approval (early April), I printed out all the documents in Chinese at a printing facility in Mudanjiang Medical University. Completed questionnaires were stored in a locked cabinet in an office of the university once they were collected from schools. During the survey, nobody had the key to the cabinet. After finishing all the fieldwork in China, I sent all the questionnaires back to the Centre for Population Health Sciences, Edinburgh University, by registered mail (China Post), where I stored the questionnaires in a secure, locked filing cabinet to keep them confidential.

3.9.2 Data coding

Epidata Data Entry software (Epidata Association, http://www.epidata.dk) was used to code and enter data. First, a sample of the questionnaire was recorded in Epidata format (a '.qes' file), which defined the variable names, types, and lengths, as well as the layout of the data entry form for a file. To ensure consistency between database and questionnaires and avoid potential entry errors, the Chinese version of questionnaire was used in the Epidata. Variable names were generated (eg knldg1 and atttd2) - the same variable names were used in SPSS for analysis. Responses were recorded in a '.rec' file as numbers, and the coding of responses is described in Table 3-11. For example, for knowledge questions: 'True' is 1, 'False' is 2 and 'Don't know' is 3. All missing data (participant chose not to respond) were coded accordingly. A check file ('chk'file) was used to check the validity of data during data entry. Below are the settings made in Epidata for data entry; they also include ways to reduce manual errors via computer-based management prior to data entry.

Field type: As only closed questions were included in the questionnaire, categorical fields were set for all the questions except age (numerical fields), where only numbers could be entered.

Field length: determined how many characters could be entered in one field.

- All the variables but age were categorical (the number of categories was 5), so only 1 number could be entered in these fields.
- For age, the anticipated age range was 16–19, which includes no numbers lower than 10 or higher than 99, so 2 characters could be entered.

Range/legal values: limited the values that could be entered in the field.

- All the variables but age were categorical ones, so a legal value limit was set for these categorical fields. The input needed to match the specified list of values.
- For example: Gender: 1=male, 2=female, so only 1 or 2 can be entered; Agreement: strongly disagree=1, somewhat disagree=2, somewhat agree=3, strongly agree=4, unsure=5, so only 1, 2, 3, 4 or 5 could be entered.
- I set a range limit for age, which was from 10 to 99.

Jumps: Jumps were used to move between two fields. Conditional jumps were used in the coding sheet; the first question in the questionnaire was a screening one, and if participants answered 'yes', they could go on to answer the following knowledge questions, otherwise, they needed to jump to attitude questions.

Finally, a database, based on the questionnaire, was generated (Figure 3-10 presents the database from Epidata).

3.9.3 Data entry and checking

All the data (3,788 questionnaires) was entered to the Epidata database by me first, and a colleague with data entry skills undertook a second entry of 10% of the data - 379 questionnaires (these were selected randomly on the basis of a number sequence with regular a interval - 6, 16, 26 ... 3766, 3776, and 3786). All the data entry was conducted at the University of Edinburgh, and it took approximately three months (from June to August 2013) to complete the two entries. In order to reduce manual errors,, I set up a time limit for my single data entry, which was no more than three hours a day and five days a week. Double entry of 10% of the data was done by my colleague over two weeks. Questionnaires that had been entered into Epidata were again put in the locked filing cabinet in the office.

Each questionnaire had 50 items, which meant that I need to enter 189,400 items in total. 10% of the data were checked automatically in Epidata. Below are the results of the data check:

- Double entry: 69 errors from 34 questionnaires out of 758 questionnaires (combining the two data sets – my colleague's 's and mine) were found, and the overall discrepancy rate was 0.18% per field (item) (calculation equation: 69 errors / 18,950 items).
- Single entry (first data entry by me): 23 errors from 42 questionnaires were found in 378 questionnaires, and the error rate was 0.22% per field (item) (calculation equation: 42 errors / 18,950 items)
- Single entry (second data entry by my colleague): 27 errors from 11 questionnaires were found, and the error rate for the second data entry is 0.14% (calculation equation: 27 errors / 18,950 items).

The error rate (0.14%–0.22%) for single data entry was acceptable when compared with international studies (detailed discussion is addressed in Chapter 4).

All the mistakes were typically mistyping or complete omission.

3.10 Approach to data analysis

In common with most questionnaire-based surveys, my data analysis was intended to produce simple frequencies for each of my questionnaire variable, and to look for associations between variables.

Hence, I firstly used descriptive analysis to demonstrate the characteristics of respondents in terms of demographics, smoking, and schools, and also the proposed 'dependent variables': level of awareness, knowledge, acceptability, and attitudes. Note that I used some variables (such as knowledge) as both predictor and outcome variables (see below). Second, I used a simple measure of association (chi-square testing) to initially explore the relationship between predictor and outcome variables. Third, I used logistic regression to explore the association between multiple variables – this enabled me to take account of confounding effects. Outcome variables were categorical, and I used a multivariate logistic regression approach. Finally, to avoid multiple testing issues, I used factor analysis to transform the attitudinal variables before undertaking logistic regression to explore the association among them. Details of my analysis methods are described below.

3.10.1 Analysis plan

My main questions were:

- what is the level of knowledge of, acceptability of, and attitudes towards HPV?
- how do demographics affect knowledge of, acceptability of, and attitudes towards HPV?
- what is the association between knowledge and acceptability, attitudes and acceptability, and knowledge and attitudes?

My analytical techniques (and their associated research questions) were:

Descriptive analysis (percentage displayed)

- what are the characteristics of participants (age, gender, rurality, smoking, and school)?
- what is the awareness of HPV and acceptability of HPV vaccination (age, gender, rurality, smoking, and school)?
- what is the level of knowledge of HPV, cervical screening, and HPV vaccination?
- what are the attitudes towards HPV, cervical screening, and HPV vaccination?

Chi-square testing analysis (cross tabs)

Participants were categorised into an aware/unaware of HPV subgroup, male/female subgroup, urban/rural subgroup, and a <18 / >=18 age subgroup. Results are shown by category.

- what are the differences in demographics, attitudes, and acceptability between respondents who have heard of HPV and those who have not?

- what is the influence of age, gender, and rurality on the following variables?
  - knowledge level of HPV (population: people who knew of HPV)
  - perceived risk and severity of HPV and cervical cancer
  - attitudes to the potential stigma of HPV
  - perceived benefits of and barriers to vaccination
  - others' influences on the acceptability of the vaccine

Factor analysis—exploratory factor analysis

What are the attitude patterns extracted from the attitudes items?

Logistic regression analysis (outputs are expressed as odds ratios)

What are the predictors for acceptability and knowledge?

- Association between acceptability and attitudes (population: all respondents)
- Association between attitudes and knowledge, acceptability and knowledge (population: people who know about HPV

3.10.2 Statistical methods

Descriptive analysis and chi-square testing

Descriptive statistical analysis was used to summarise demographic characteristics. Categorical variables were presented as numbers and percentages (eg acceptability). Associations were initially identified using chi-square testing. As responses to attitude questions used a five-level Likert scale (strongly disagree, somewhat disagree, somewhat agree, strongly agree, unsure), the numbers in each box of the chi-square table were very likely to be less than 5 (which is too small for meaningful analyses). Accordingly, I regrouped the 5-Likert scale response options into three categories (disagree, agree, unsure) based on the consistent meaning of similar categories (this was only for analysis of associations).

Factor analysis

Two key steps were included in my factor analysis. First, I decided on how many factors could be extracted from attitudinal variables to achieve the best estimate of the original groupings of variables. Second, I decided on which individual variables could be included in the specific factor to find the variables most matched with the factor. . The *eigenvalue* is used to determine the number of factors extracted, and *factor loadings* determine the percentage of variance of the individual variable that can be explained by the factor. The

Varimax rotation model is used to determine how many factors are formulated, to achieve the best match between the factor and the grouping of variables (maximising the variance of a factor on the variables) - and to make the output more understandable.

I chose principal component factor analysis [232, 233] to identify attitude patterns. This is a widely used method for factor extraction which extracts the maximum possible variance. To determine the number of factors, I considered potential candidate factors as those with an eigenvalue greater than 1.0. When a factor has eigenvalue smaller than 1.0, the factor's explanatory power is lower than the power of the original variable, and the factor is assumed not to be the best estimate of the original grouping of variables [233]. Accordingly, factors with smaller eigenvalues (< 1.0) were removed. But the final included factors also depended on their importance in the context of my thesis topic.

Individual variables that had 0.40 factor loadings were included in the factor [233]. In factor analysis, '0.70 factor loadings' describe a situation in which half of the variance of the individual variable can be explained by the factor [232, 233]. However, the 0.70 loading is a high standard, and most data may not meet this criterion, thus, '0.40 loadings' serve as a commonly used standard [232] [233].

Factors were finally recorded and saved as factor scores, which are continuous variables, for use as variables in the subsequent modelling. Factor scores were then categorised into quartiles according to the distribution of the subjects. Figure 3-11 shows the key elements of my factor analysis.

Logistic regression

Logistic regression analysis was used to determine the association between variables taking potential confounders into account – analyses included attitude (predictor) and acceptability, and attitude (predictor) and level of knowledge (low level and high level). Odds ratios (OR's) were estimated between each quartile (except the lowest one) and the lowest quartile of each attitude pattern (predictor) with respect to the outcomes (acceptability or level of knowledge). The logistic regression model was also adjusted for age, gender, and rurality. All analyses were two sided at the 2.5% level ($p<0.025$) as the statistically significant value.

I undertook some data manipulation. For example, to examine the associations between knowledge level and predictor variables responses to knowledge questions were recorded as scores. If the respondents chose the right answer, they would be given a score of 1; if they chose the wrong answer, they would be given a score of -1; if they didn't know the answer, they would be given a score of 0. Theoretically, the lowest possible score for all the knowledge questions is -14, while the highest score is 14. As it transpired, the lowest score was -6, and the highest was 14. The median was 6. I classified the responses into two categories: high level of knowledge (>6 score) and low level of knowledge (≤6 score). Finally, I categorised 222 respondents with a 'high level of knowledge' and 255 respondents with a 'low level of knowledge'.

Handling of the predictor variables

In the initial analysis, I found that gender and rurality had an influence on knowledge and acceptability of HPV vaccination. In order to identify the influence of attitudinal variables (eg stigma, perceived barriers), adjustments for gender and rurality were made.

Predictor variables including stigma, perceived barriers, and perceived risk were extracted as 'factors' based on my factor analysis. Factor scores were recorded during this process. Factor scores were continuous variables and represented the ratings of participants' responses. In order to easily estimate the associations, factor scores were categorised into quartiles according to the distribution of the study subjects. Thus, predictors extracted from the factor analysis were all categorical variables.

Handling of the outcome variables

Level of knowledge of HPV was recorded as 'high score knowledge' or 'low score knowledge' based on the number of 'correct' answers—so level of knowledge was a dichotomous outcome variable. Acceptability was recorded as one of three points on a Likert scale.

3.10.3 Conclusion

I used statistical methods to produce summary statistics and explore associations between variables. Of course, demonstration of statistical association does not imply causality; any demonstrated association needs to make sense. Hence, the discussion section of my results chapter explains more what the results mean and how reliable, or plausible, they might be.

3.11 Rationale for my chosen statistical methods

3.11.1 Factor analysis (exploratory factor analysis)

Two main issues occur in the process of analysing associations between a large number of similar variables. They are the main reasons why I undertook the factor analysis prior to the regression analysis.

The first issue concerns the likely collinearity or multicollinearity within the variables. In order to demonstrate an association in a robust way, I wanted to use a regression model that gave valid results. Ideally, the best regression models have predictor variables that each correlate highly with the outcome variable rather than correlating with each other (or only minimal correlation). However, there were 20 questions generated from five concepts relating to attitudes towards HPV vaccination in the questionnaire. It is inevitable that these questions (variables) correlate in some ways. For example, questions like ‘Do you agree that people will think someone who is infected with HPV is likely to have been promiscuous?’ and questions like ‘Do you agree people are infected with HPV because they or their partners have been unfaithful?’ would have some kind of correlation, meaning that people who choose the ‘promiscuous’ opinion would also be more likely to believe the ‘unfaithful’ statement. And when the two are used to identify the association with the level of knowledge respectively, the result of each variable would be difficult to explain if it was affected by another in some way. Hence, when these variables are directly included in the statistical analysis, issues of collinearity may occur, or of multicollinearity, when three or more predictor variables share the same theme.

The second issue relates to multiple testing. I aimed to analyse the association between attitudes and level of knowledge, and attitudes and the acceptability of HPV vaccines. Given that I have 20 variables relating to attitudes, theoretically, I should undertake more than 20 tests to determine the associations. This inevitably produces multiple testing problems due to such a large number of association tests, and accordingly increases the probability of finding associations purely by chance.

Therefore, to avoid issues of collinearity and multiple testing, I decided to use factor analysis prior to the association analysis, in which, by linear transformation, 20 variables could be combined into a smaller number of groups of variables. This process should ideally capture the meanings in the original uncombined variables as much as possible. The ‘number’ of factors refer to the number of groups of original variables. Given that the attitude questions were generated based on the Health Belief Model (containing five constructs), theoretically, five factors (groups of variables) at least would be extracted via factor analysis. This may tackle the collinearity problems and reduce the multiple testing issues to some extent via decreasing the number of variables.

3.11.2 Logistic regression

I also sought, in my analysis, to examine associations between key variables using logistic regression techniques.

- My key outcome variables were: 1) level of knowledge about HPV and 2) acceptability of HPV vaccine.
- My key predictor variables were age, gender, rurality, perceived stigma, perceived risk, perceived benefits, perceived severity, and perceived barriers.

Logistic regression analysis is used to identify the association between a 'dependent', or outcome variable and multiple independent variables – it seeks to tease out the independent contribution of independent variables on outcome. Two scenarios can be accommodated with regression methods:

- The dependent variable is continuous; multiple linear regression is generally used.
- The dependent variable is categorical (as is the case with my data); chi-square testing is appropriate in the first instance, then binary or multivariate logistic regression.

In the presence of confounders which would influence the association between variables, logistic regression is usually used for adjustment.

In terms of the dichotomous and multiple dependent variables, I used binary and multivariate logistic regression analysis respectively. In my survey, I used multivariate logistic regression to identify the relationship between predictors and level of knowledge, and predictors and acceptability.

3.12 Ethics Review in UK and China

The study underwent a rigorous ethics review at Edinburgh University – through the Centre for Population Health Sciences's ethics panel. The feedback I received included issues over inclusion of questions about sexual activity, age group selection, the balance of how much information on HPV was given prior to completion of the questionnaire, and inclusion of individual socio-economic data in the questionnaire. There was some dialogue between my study team (myself and my supervisors) and the ethics committee over pragmatic considerations, maintaining the integrity of international study comparisons, and the Chinese research environment (which is fundamentally different from the UK research environment - see Appendix 6, which provides the ethical documents. Following some modification of my protocol, ethical approval was obtained.

I also needed ethical approval from a Chinese institution; with this in mind I established a dialogue over this project with an epidemiology professor (Professor Li Xiaoxia) in Mudanjiang Medical University - the local university in Mudanjiang city. She agreed to help us in the ethics review and the storage of questionnaires. She helped us to review the documents and submit them to the ethics committee of Mudanjiang Medical University – approval was duly granted. Professor Li provided extremely useful input on local implementation issues, highlighting levels of sexual health education in Mudanjiang city, and strategies for avoiding bias in questionnaire distribution. No further changes were suggested in terms of the content or structure of the questionnaire or conduct of the survey.

3.13 Conclusion

This chapter has described the methods I used in my questionnaire survey, including the development of the instrument, recruitment, data management, and analysis. I have given particular emphasis to the steps taken to ensure the sample is as representative of the target population as possible. I have acknowledge the limitations in the representativeness of my sample – nevertheless, while no sampling technique is perfect, I feel I have a sample from which implications for the wider Chinese population can reasonably be drawn.

Development of the survey was strongly influenced by my literature review and discussions with my supervisors - and a statistician within the Centre for Population Health Sciences. I drew on theoretical frameworks in developing my survey (including the Health Belief Model), and used established techniques such as concurrent probing, and think-aloud interviewing in my cognitive testing. Data collection was a very significant task; it included sample size estimation, evaluation of the representativeness of Heilongjiang province, selection of schools, classes, and students, implementation of the survey and data coding, entry, and double checking.

I am hopeful this process has produced results which are valid and meaningful – they are presented in the following chapter.

Table 3-1: Modes of administration of the survey

Mode of distribution	Pros	Cons
Postal questionnaire	• Affordable, the cost only consists of printing and distributing • Flexible, respondents have more time to think, and would give more a honest reply due to the absence of the interviewer	• Poor response rate, only a very few people would be interested in filling out the questionnaire and mailing it back • Questions can be misunderstood • Inconvenient in China where many people live in communities that rarely use the postal box, so it is hard to reach people in the community by post
Face to face administration in community	• Researchers can clarify the doubt and ensure questions are properly understood • Respondents are randomly distributed, and there is no selection bias;	• Time consuming: it will take a long time to reach a great many people • Expensive: it will cost much for the administration
High school	• Convenient, it could reach large amount of people in short time • Affordable, the cost only consists of printing • High response rate, when the questionnaire is distributed in class	• Selection bias: this will ignore those adolescents who do not attend high schools, especially in rural regions • Social desirability bias: adolescents would response conforming to the social norms when the researchers are present
College or university	• Big sample size, it would reach a big sample size in short time • Affordable, the cost is low, only consist of printing • High response rate if distributed via class	• Selection bias: this will ignore the young adults who do not attend college or university, especially those from rural areas • Social desirability bias
Health centre/ hospital	• Convenient, it's easy to reach patients in the hospitals • Affordable, the cost is low	Selection bias: patients who go to hospital would be those who care more about health

Table 3-2: Comparison of Health Behaviour Theories

Theories	Level	Purpose	Elements/Constructs					Scenarios (some examples)
			Positive/negative aspects of the behaviour	Other people's support	One's ability to perform the behaviour	One's risk if not engaged in the behaviour	One made a firm commitment to engage in the behaviour	
HBM	Individual	Explanatory Theory	Benefits, barriers	Cues from media, friends	Self-efficacy	Perceived risk/severity	NA	cancer screening injury prevention
TRA	Interpersonal	Explanatory Theory	Behavioural beliefs	Subjective norms	NA	NA	Behavioural intentions	tobacco use following clinician recommendations
TPB	Interpersonal	Explanatory Theory	Behavioural beliefs	Subjective norms	Perceived behavioural control	NA	Behavioural intentions	tobacco use following clinician recommendations
SCT	Interpersonal	Explanatory Theory	Outcome expectations	Social support	Self-efficacy	Emotional coping responses	Self-control	eating habits contraception
TTM	Individual	Change Theory	Pros, cons	Helping relationships	Self-efficacy	Dramatic relief	Self-liberation	cancer screening domestic violence

HBM: Health Belief Model
TRA: Theory of reasoned action
TPB: Theory of Planned Behaviour
SCT: Social Cognitive Theory
TTM: Transtheoretical Model
[210-214]

Table 3-3: Stages and elements for sample size estimation

Research questions (rank)	The primary objective	What is the level of knowledge of HPV in the teenage participants	
	The primary, secondary, and tertiary comparison of interest	What is the association between gender and level of knowledge	
		What is the association between the level of knowledge of HPV and the acceptability of vaccination	
		What is the association between attitudes towards HPV and the acceptability of vaccination	
Main elements	The outcome and predictor variables	Outcome variables	Predictor variables
		Knowledge	Age, gender, rurality and smoking
		Attitudes	Age, gender, rurality and smoking
			Awareness of HPV (those who know and those who do not)
			Knowledge level
		Acceptability	Age, gender, rurality and smoking
			Awareness of HPV (those who know and those who do not)
			Knowledge level
			Attitudes
	Parameter estimates (on which sample size based)	Parameter symbols	Parameter meanings
		α	Significance level (probability of committing a type I error)
		Power (1- β)	Probability of making a type II error
		p1, p2, q1, q2	Frequency of the outcome
		$p_1 - p_2$	Difference in proportions of the outcome
		r	Ratio of larger group to smaller group
		Variability	Potential variables will confound the association between predictors and outcomes
Prior studies (Data on which I based my assumptions)	Primary comparison	Gender difference is 15%: 50% males know HPV causes cervical cancer, and 35% females do not	
	Secondary comparison	Acceptability difference is 15%: acceptability is 60% and 75% between people who have knowledge and those who do not	
Statistical tests used	Test	Role of test	
	Chi-square test	To identify age, gender, and rurality influence on knowledge, attitudes, and acceptability	
	Logistic regression	To identify association between acceptability and knowledge, acceptability and attitudes, attitudes and knowledge	
	Factor analysis	To extract factors from 20 attitudinal variables	
	Adjust for covariates	To control confounding and bias	

Table 3-4: Parameters that affect sample size estimation

Parameters on which sample size based		Require smaller Sample Size	Require larger Sample Size
Indicators on which sample size calculation formula based	Strength of the association	Moderate	Very small
	Frequency of the outcome	Moderate	Very small
	How precise I want to be (confidence level)	Fairly precise	Very precise
	How sure I want to be (statistical power)	Fairly sure	Very sure
How much variation in the study population (potential confounding)		Low variation	High variation
Response rate		High rate	Low rate
Missing data		Few missing	More missing

Table 3-5: Demography of provinces in China in 2011

Rankings of population	Province	Population (10 thousand)	Proportion of urban population (%)
1	Guangdong	10505	63.4
2	Shandong	9637	48.3
3	Henan	9388	37.7
4	Sichuan	8050	38.7
5	Jiangsu	7899	55.6
6	Hebei	7241	43.0
7	Hunan	6596	43.2
8	Anhui	5968	42.1
9	Hubei	5758	46.0
10	Zhejiang	5463	57.9
11	Guangxi	4645	39.2
12	Yunnan	4631	34.0
13	Jiangxi	4488	43.2
14	Liaoning	4383	60.4
15	**Heilongjiang**	**3834**	**55.5**
16	Shaanxi	3743	43.5
17	Fujian	3720	51.4
18	Shanxi	3593	46.0
19	Guizhou	3469	29.9
20	Chongqing	2919	51.6
21	Jilin	2749	53.3
22	Gansu	2564	32.7
23	Inner Mongolia	2482	53.4
24	Shanghai	2347	88.6
25	Xinjiang	2209	39.9
26	Beijing	2019	85.0
27	Tianjin	1355	78.0
28	Hainan	877	49.1
29	Ningxia	639	46.1
30	Qinghai	568	41.9
31	Tibet	303	23.8

Reproduced from *China Population Census 2010, China Statistics Yearbook 2012[149],* and *China Health Statistical Yearbook 2011 [223]*

Table 3-6: GDP of provinces in China in 2011

Rankings of GDP per capita	Province	GDP per capita (RMB)	GDP (100 million RMB)
1	Tianjin	84337	11191.0
2	Shanghai	82560	19195.7
3	Beijing	80394	16011.4
4	Jiangsu	61649	48604.3
5	Zhejiang	58665	32000.1
6	Inner Mongolia	57515	14246.1
7	Liaoning	50299	22025.9
8	Guangdong	50295	52673.6
9	Shandong	47260	45429.2
10	Fujian	46972	17410.2
11	Jilin	38321	10530.7
12	Chongqing	34500	10011.1
13	Hubei	34131	19594.2
14	Hebei	33571	24228.2
15	Shaanxi	33142	12391.3
16	**Heilongjiang**	**32615**	**12503.8**
17	Ningxia	32392	2060.8
18	Shanxi	30974	11100.2
19	Hunan	29828	19635.2
20	Xinjiang	29496	6474.5
21	Henan	28981	27232.0
22	Qinghai	28891	1634.7
23	Hainan	28797	2515.3
24	Sichuan	26133	21026.7
25	Jiangxi	25884	11583.8
26	Anhui	25340	15110.3
27	Guangxi	25315	11714.4
28	Tibet	20077	605.8
29	Gansu	19517	5000.5
30	Yunnan	18957	8751.0
31	Guizhou	16413	5701.8

Reproduced from *China Statistics Yearbook 2012[149]*, and *China Health Statistical Yearbook 2011[223]*

Table 3-7: Health care expenditure in provinces of China in 2010

Urban regions				Rural regions			
Rankings#	Provinces	Health care expenditure per capita (RMB)	Proportion*	Rankings#	Provinces	Health care expenditure per capita (RMB)	Proportion*
1	Beijing	1389.5	7.8	1	Beijing	867.9	9.8
2	Tianjin	1273.4	8.6	2	Shanghai	738.9	7.5
3	Jilin	1120.4	10.3	3	Zhejiang	609.1	7.9
4	Liaoning	1018.4	8.3	4	Jilin	511.5	13.1
5	Shanghai	1002.1	4.8	**5**	**Heilongjiang**	**434.3**	**10.2**
6	Inner Mongolia	992.7	8.0	6	Inner Mongolia	416.9	10.5
7	Zhejiang	984.6	5.9	7	Liaoning	409.6	9.6
8	Chongqing	982.7	8.1	8	Ningxia	356.4	10.6
9	**Heilongjiang**	**978.8**	**10.2**	9	Shaanxi	329.3	9.8
10	Hebei	971.3	10.0	10	Jiangsu	323.0	5.6
11	Guangdong	925.6	5.5	11	Xinjiang	316.6	10.7
12	Ningxia	921.9	9.0	12	Shandong	301.6	6.8
13	Shandong	885.2	7.4	13	Tianjin	299.8	7.0
14	Henan	875.5	9.2	14	Qinghai	291.3	9.1
15	Shaanxi	863.4	8.1	15	Hebei	289.3	8.6
16	Jiangsu	808.4	6.1	16	Hunan	258.1	6.4
17	Shanxi	789.9	8.4	17	Sichuan	258.1	6.2
18	Hunan	784.7	7.2	18	Henan	242.9	7.2
19	Gansu	746.8	8.4	19	Chongqing	242.6	7.7
20	Anhui	716.9	7.0	20	Shanxi	240.9	7.3
21	Yunnan	708.8	6.9	21	Hubei	236.3	6.3
22	Qinghai	701.4	8.0	22	Jiangxi	232.8	6.6
23	Hubei	694.6	6.7	23	Guangdong	232.0	4.6
24	Xinjiang	684.0	7.3	24	Anhui	227.1	6.2
25	Sichuan	648.3	6.0	25	Fujian	219.0	4.4
26	Hainan	604.2	6.0	26	Guangxi	205.2	6.3
27	Fujian	591.5	4.4	27	Yunnan	197.6	6.8
28	Jiangxi	550.3	5.6	28	Gansu	180.1	6.5
29	Guangxi	538.2	5.2	29	Guizhou	133.2	5.5
30	Guizhou	535.4	5.9	30	Hainan	129.3	4.2
31	Tibet	352.3	3.9	31	Tibet	71.5	3.0

Rankings based on the health care expenditure per capita
*Proportion of health care expenditure in total consumption expenditure
Reproduced from *China Health Statistical Yearbook 2011[223]*

Table 3-8: Standardised death rate of cervical cancer in provinces in China in 2004–2005 [17]

Rankings	Province	Standardised death rate of cervical cancer (per 100,000 population)
1	Xinjiang	10.69
2	Gansu	9.36
3	Hunan	4.98
4	Jiangxi	4.9
5	Shaanxi	4.59
6	Ningxia	4.21
7	Guizhou	3.99
8	Qinghai	3.9
9	Shanxi	3.7
10	Tibet	3.38
11	Anhui	2.81
12	Guangxi	2.77
13	Henan	2.73
14	Hainan	2.65
15	Hubei	2.5
16	Hebei	2.35
17	Zhejiang	2.29
18	**Heilongjiang**	**2.12**
19	Tianjin	2.11
20	Fujian	2.01
21	Jilin	1.97
22	Yunnan	1.78
23	Guangdong	1.73
24	Inner Mongolia	1.61
25	Sichuan	1.53
26	Liaoning	1.35
27	Beijing	1.28
28	Shandong	1.23
29	Jiangsu	1.2
30	Shanghai	1.04
31	Chongqing	1.02

Table 3-9: Overview of Heilongjiang province in China [17, 149, 223]

	China	Heilongjiang province	Similar conditions in other parts of China (31 provincial regions)	Rank of Heilongjiang in China (31 provincial regions)
Demography				
Population (million)	1,300M	38M	9 provinces (30-50M)	Top 15th populated
Proportion of rurality (%)	54%	44.5%	17 provinces (40-60%)	Top 9th urbanised province
Economic development				
GDP per capita (¥) 2011	32615 (median)	32,615	8 provinces (¥30,000-40,000)	Top 16th wealthy
Household income (¥) (urban vs. rural) 2010	18373 vs. 6604 (median)	15,696 vs.7,590	10 provinces (<¥18,000)	Top 28th vs. Top 10th wealthy
Health care				
Health expenditure per capita (¥) (urban vs. rural) 2010	808 vs. 258 (median)	978 vs. 434	11 provinces (¥ 800-1,000)	Top 9th vs. Top 5th most
Out-of-pocket proportion in total consumption (%) (urban vs. rural) 2010	6.4% vs. 8.4%	10.2% vs. 10.2%	3 provinces (>10%) vs. 5 provinces (>10%)	Top 2nd vs. Top 5th most
Education				
Illiteracy rate (%) 2010	3.8% (median)	2.1%	16 provinces (1.7-4.0%)	Top 8th least illiteracy
Cervical cancer				
Cervical cancer mortality (2004-2005)	2.35/100,000 (median)	2.12/100,000	10 provinces (1.5-2.5)	Top 14th low mortality

Table 3-10: Timeline of the survey

Time	Visit	School
Mar 20th – Apr 5th	1st visit	All five high schools
Apr 8th –Apr 16th	2nd, 3rd, visit	Hailin high school
Apr 18th – May 1st	2nd, 3rd, visit	Ning'an high school
May 2nd – May 8th	2nd, 3rd, visit	No. 3 high school
May 9th – May 16th	2nd, 3rd, visit	No. 2 high school
May 17th – May 24th	2nd, 3rd, visit	No. 1 high school

Table 3-11: Data coding for knowledge questions and responses

	Codes for responses				
Knowledge questions' responses	True	False	Don't know		
	1	2	3		
Attitude questions' responses	Very unlikely	Somewhat unlikely	Somewhat likely	Very likely	Unsure
	1	2	3	4	5
	Strongly disagree	Somewhat disagree	Somewhat agree	Strongly agree	Unsure
	1	2	3	4	5
Demographic questions' responses	Male	Female			
	1	2			
Smoking question's response	Never	Once or twice	Used to, given up	Sometimes	Everyday
	1	2	3	4	5
High school question' response	No. 1 school	No. 2 school	No. 3 school	Ning'an school	Hailin school
	1	2	3	4	5

Figure 3-1: Flow diagram of conduct of my questionnaire survey

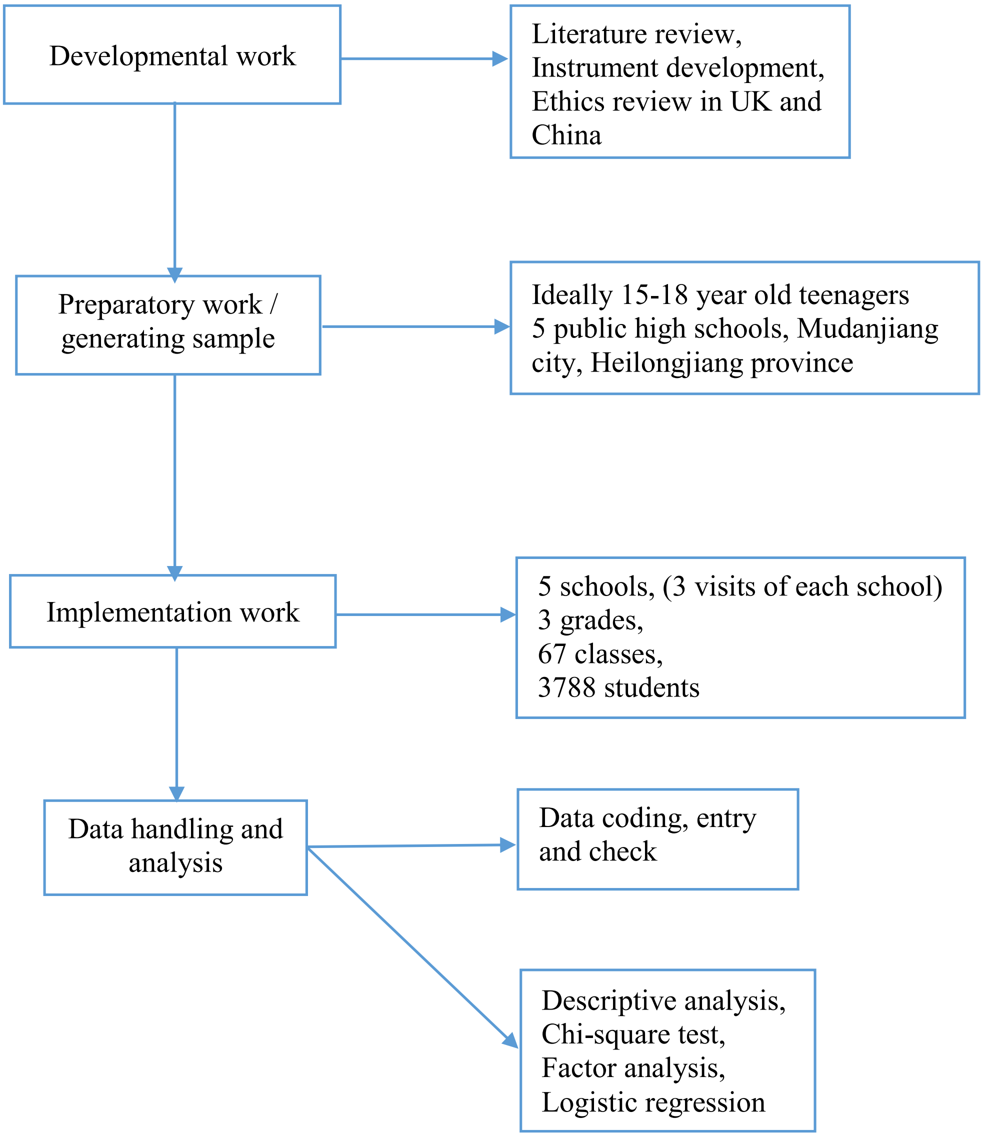


Figure 3-2: Flow diagram of my instrument development

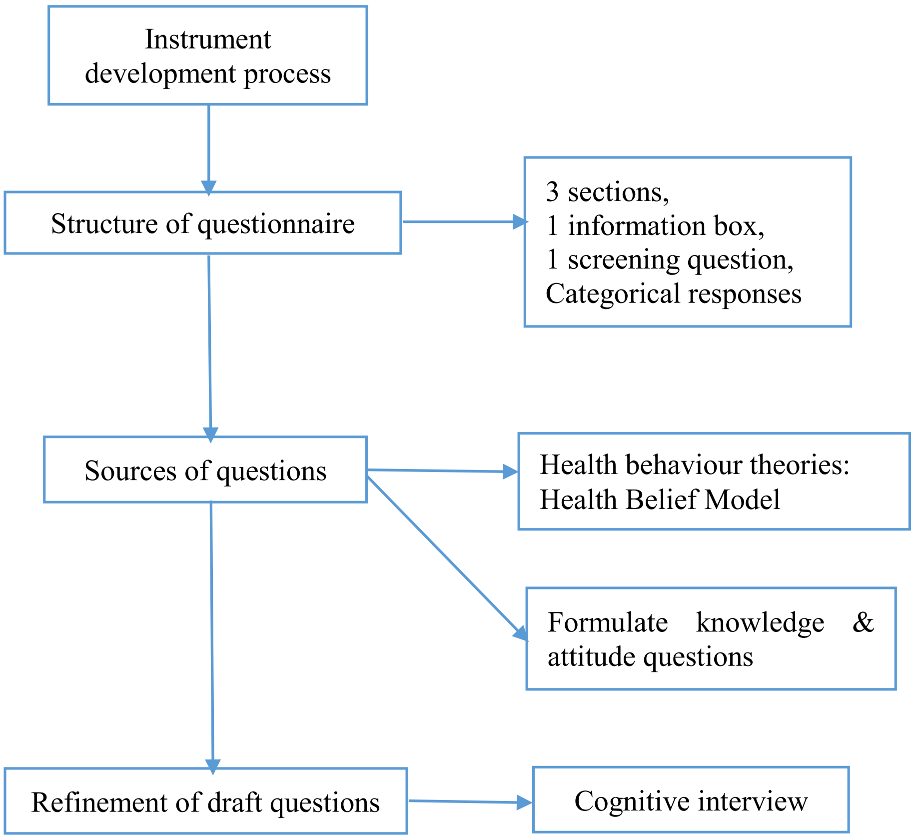
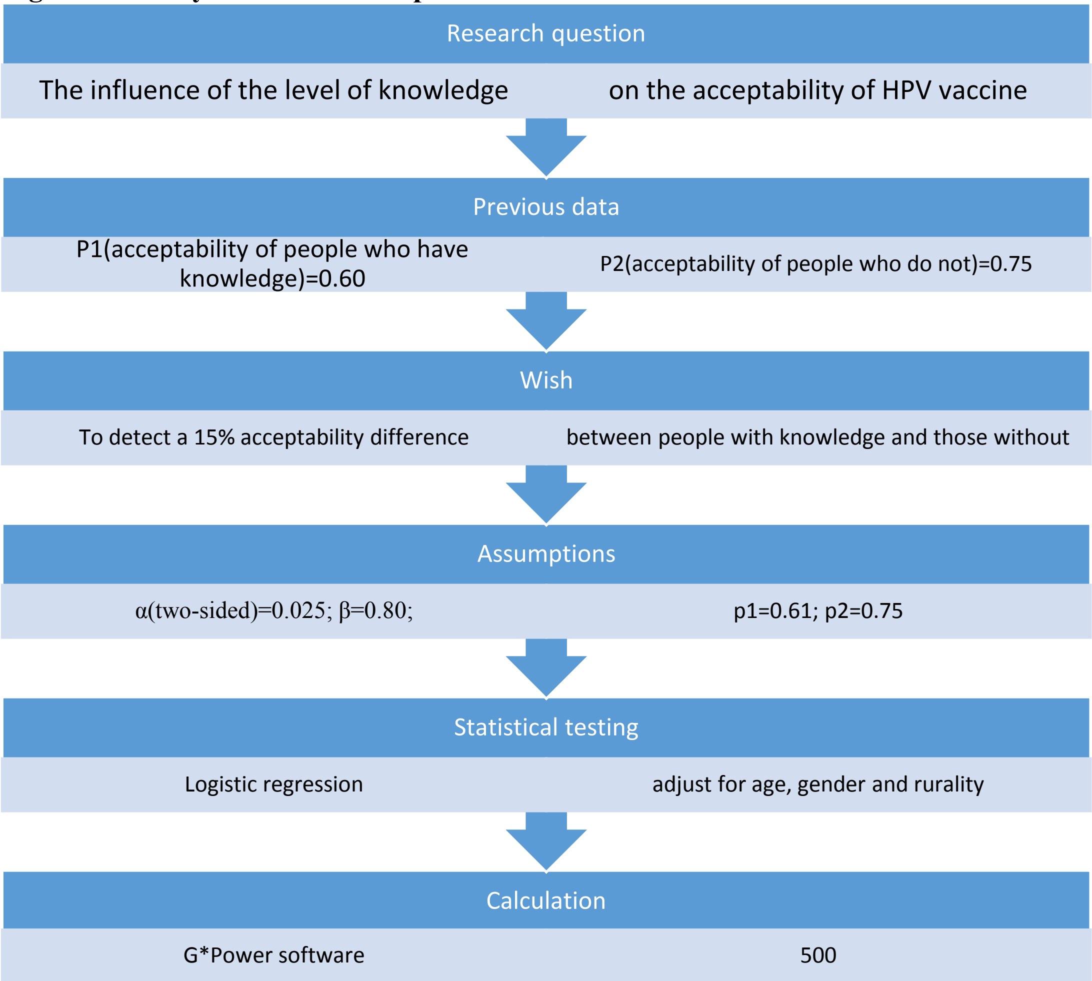
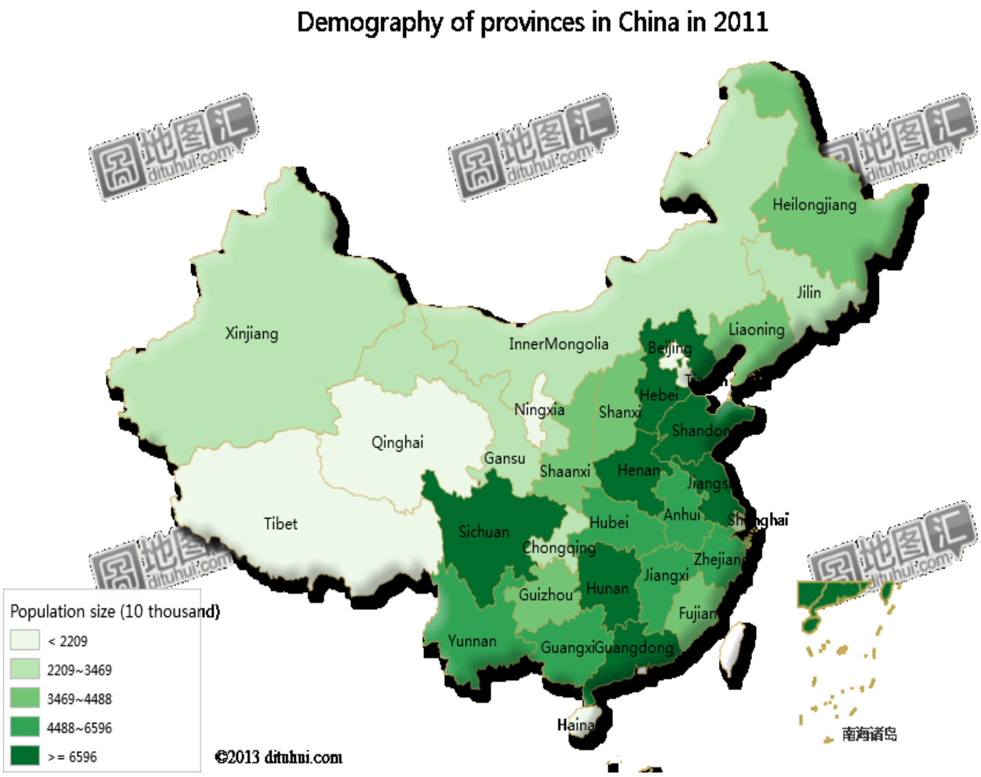


Figure 3-3: Key elements of sample size estimation



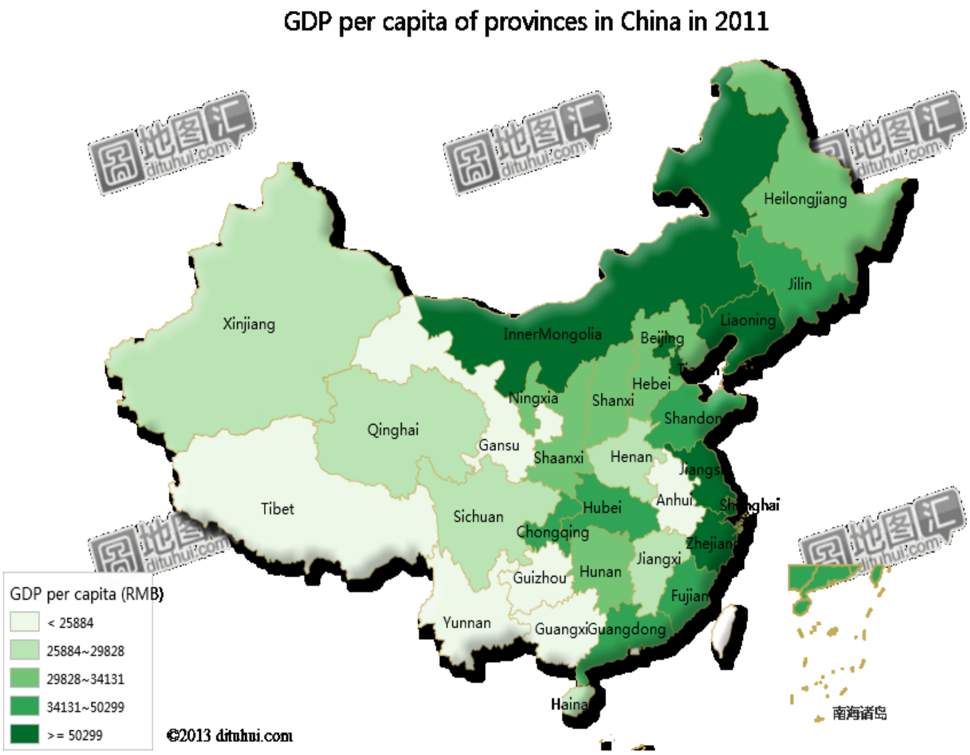
This is based on the secondary comparison of interest (other estimation of comparisons would be the same as this one)

Figure 3-4: Demography of provinces in China in 2011 [149, 223]



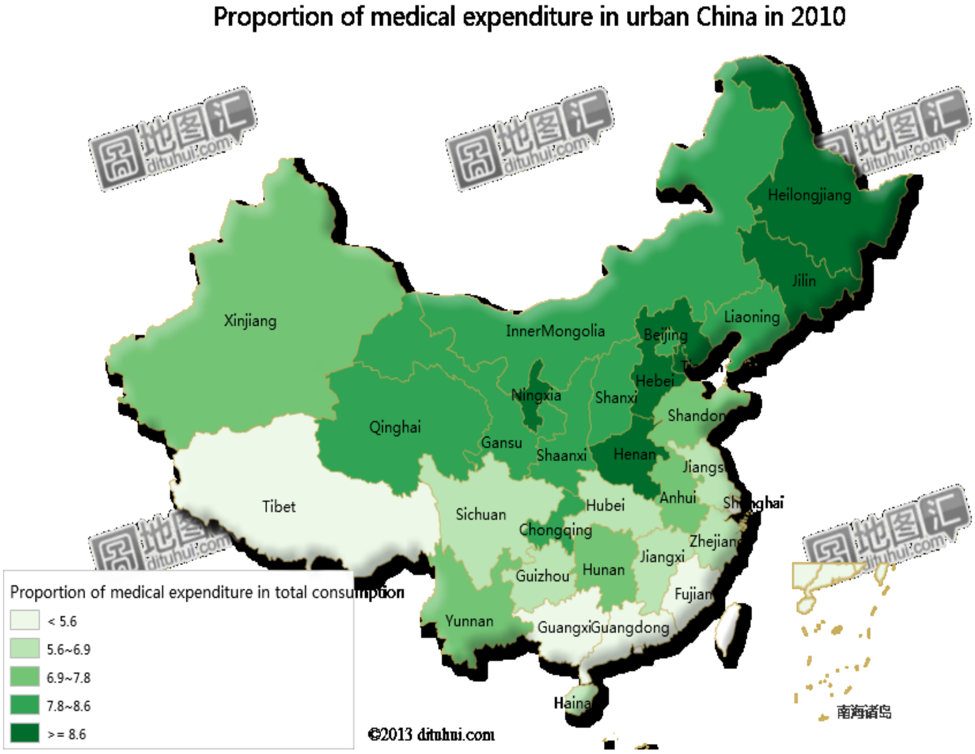
The measurement of population size is categorised into five levels (smallest to largest)

Figure 3-5: GDP per capita of provinces in China in 2011 [149, 223]



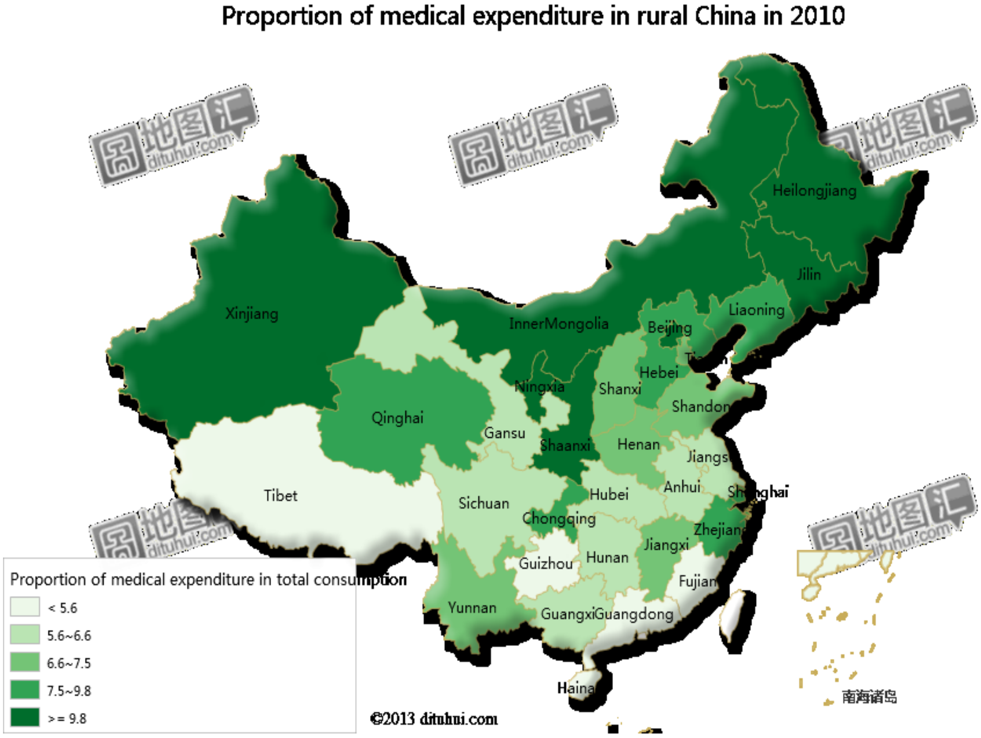
The measurement of GDP per capita (RMB) is categorised into five levels (lowest to highest)

Figure 3-6: Proportion of medical expenditure in total consumption expenditure in urban China in 2010 [223]



The measurement of health care expenditure proportion is categorised into five levels (lowest to highest)

Figure 3-7: Proportion of medical expenditure in total consumption expenditure in rural China in 2010 [223]

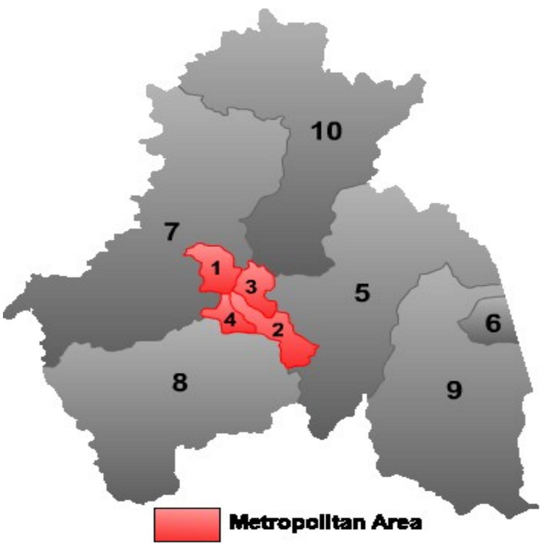


The measurement of health care expenditure proportion is categorised into five levels (lowest to highest)

Figure 3-8: Map of China: location of Heilongjiang province in China.

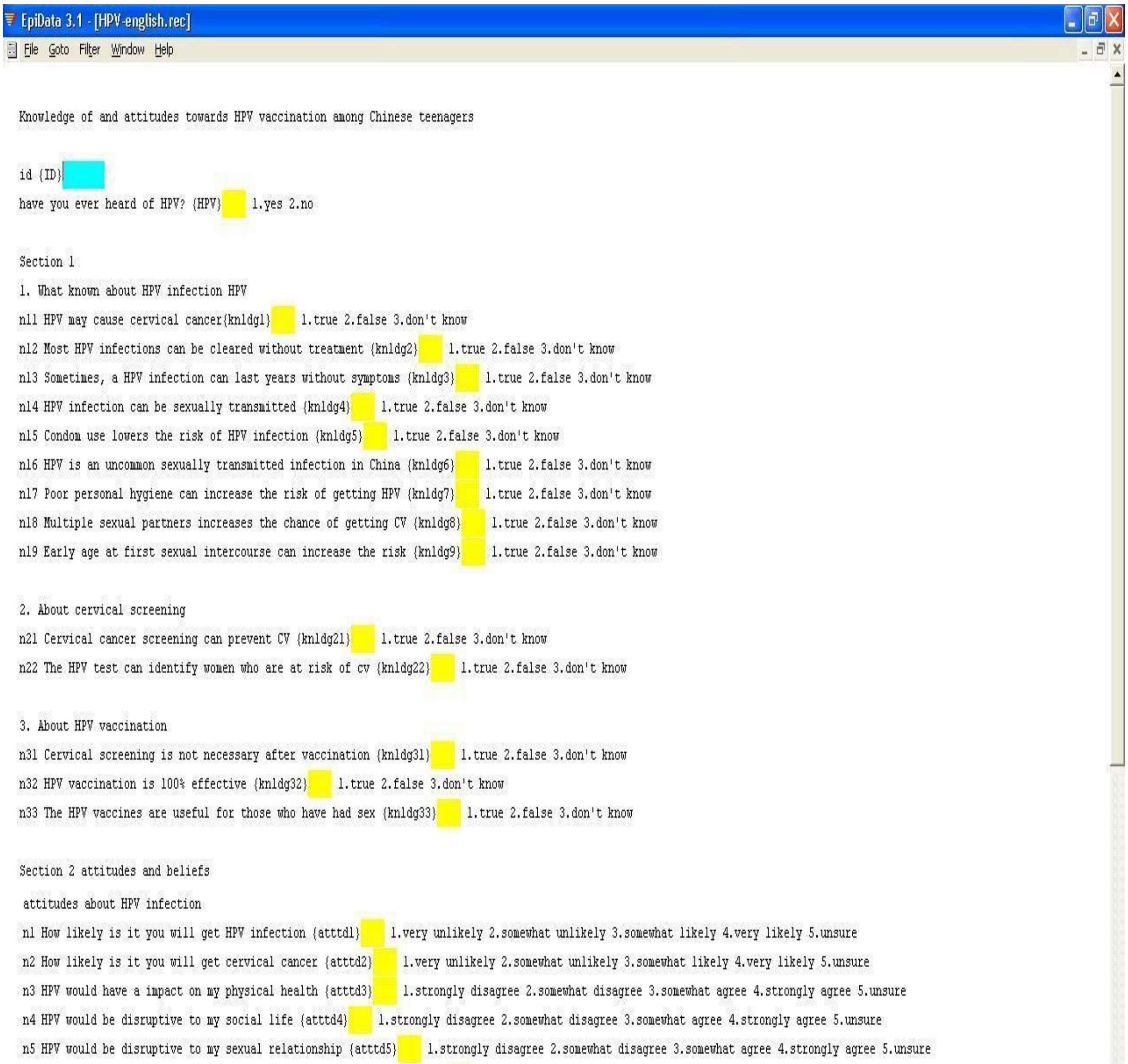
The orange region refers to Heilongjiang province; the red region refers to Mudanjiang city.

Figure 3-9: Map of Mudanjiang city: location of city centre and Hailin and Ning'an county.



The red regions refer to the central regions of the city; number 7 refers to Hailin county; number 8 refers to Ning'an county.

Figure 3-10: Database of the survey in Epidata



EpiData 3.1 - [HPV-english.rec]

File Goto Filter Window Help

Knowledge of and attitudes towards HPV vaccination among Chinese teenagers

id {ID}

have you ever heard of HPV? {HPV} 1.yes 2.no

Section 1

1. What known about HPV infection HPV

n11 HPV may cause cervical cancer{knldg1} 1.true 2.false 3.don't know

n12 Most HPV infections can be cleared without treatment {knldg2} 1.true 2.false 3.don't know

n13 Sometimes, a HPV infection can last years without symptoms {knldg3} 1.true 2.false 3.don't know

n14 HPV infection can be sexually transmitted {knldg4} 1.true 2.false 3.don't know

n15 Condom use lowers the risk of HPV infection {knldg5} 1.true 2.false 3.don't know

n16 HPV is an uncommon sexually transmitted infection in China {knldg6} 1.true 2.false 3.don't know

n17 Poor personal hygiene can increase the risk of getting HPV {knldg7} 1.true 2.false 3.don't know

n18 Multiple sexual partners increases the chance of getting CV {knldg8} 1.true 2.false 3.don't know

n19 Early age at first sexual intercourse can increase the risk {knldg9} 1.true 2.false 3.don't know

2. About cervical screening

n21 Cervical cancer screening can prevent CV {knldg21} 1.true 2.false 3.don't know

n22 The HPV test can identify women who are at risk of cv {knldg22} 1.true 2.false 3.don't know

3. About HPV vaccination

n31 Cervical screening is not necessary after vaccination {knldg31} 1.true 2.false 3.don't know

n32 HPV vaccination is 100% effective {knldg32} 1.true 2.false 3.don't know

n33 The HPV vaccines are useful for those who have had sex {knldg33} 1.true 2.false 3.don't know

Section 2 attitudes and beliefs

attitudes about HPV infection

n1 How likely is it you will get HPV infection {atttd1} 1.very unlikely 2.somewhat unlikely 3.somewhat likely 4.very likely 5.unsure

n2 How likely is it you will get cervical cancer {atttd2} 1.very unlikely 2.somewhat unlikely 3.somewhat likely 4.very likely 5.unsure

n3 HPV would have a impact on my physical health {atttd3} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n4 HPV would be disruptive to my social life {atttd4} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n5 HPV would be disruptive to my sexual relationship {atttd5} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure n6 Cervical cancer would have a impact on my physical health {atttd6} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n7 Cervical cancer would be disruptive to my social life {atttd7} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n8 Cervical cancer would be disruptive to my sexual relationship{atttd8} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

attitude about HPV vaccination

n9 How likely is it you would accept vaccination {atttd9} 1.very unlikely 2.somewhat unlikely 3.somewhat likely 4.very likely 5.unsure

n10 HPV vaccine will help them avoid HPV infection {atttd10} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n20 HPV vaccine will help them avoid cervical cancer{atttd11} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n23 It is no longer necessary to be screened for CV {atttd12} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n24 It may be appropriate to have less screening for CV {atttd13} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n25 Having a vaccination may lead to people having more sexual partners {atttd1 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n26 HPV vaccines have not been proved effective {atttd15} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n27 HPV vaccines may have side effects such as fatigue or fever {atttd16} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n28 HPV vaccines may have major side effects such as long term illness {atttd17 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n29 HPV vaccine costs too much (CNY£¤2000) {atttd18} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n30 I trust the companies that make HPV vaccines {atttd19} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n34 I would get vaccinated if my friends recommend me to do so {atttd20} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n35 I would get vaccinated if my parents recommend me to do so {atttd21} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n36 I would get vaccinated if doctors or nurses recommend me to do so {atttd22} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n37 I would get vaccinated if there is a school requirement {atttd23} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n38 I would get vaccinated if ads recommend it{atttd24} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

attitudes towards those with HPV infection

n39 Someone who is infected with HPV is is promiscuous {atttd26} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n40 If someone has HPV infection, people will gossip{atttd27} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n41 People are infected because they have been unfaithful{atttd28} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

n42 One should keep a social distance from those who are infected {atttd29} 1.strongly disagree 2.somewhat disagree 3.somewhat agree 4.strongly agree 5.unsure

Section 3 questions about you

n43 what is your gender?{gender} 1.male 2.female

n44 what is your age?{age}

n45 which of the following best describe you?{smoke} 1.never tried smoking 2.tried smoking once or twice 3.have given up 4.smoke some days 5.smoke every day

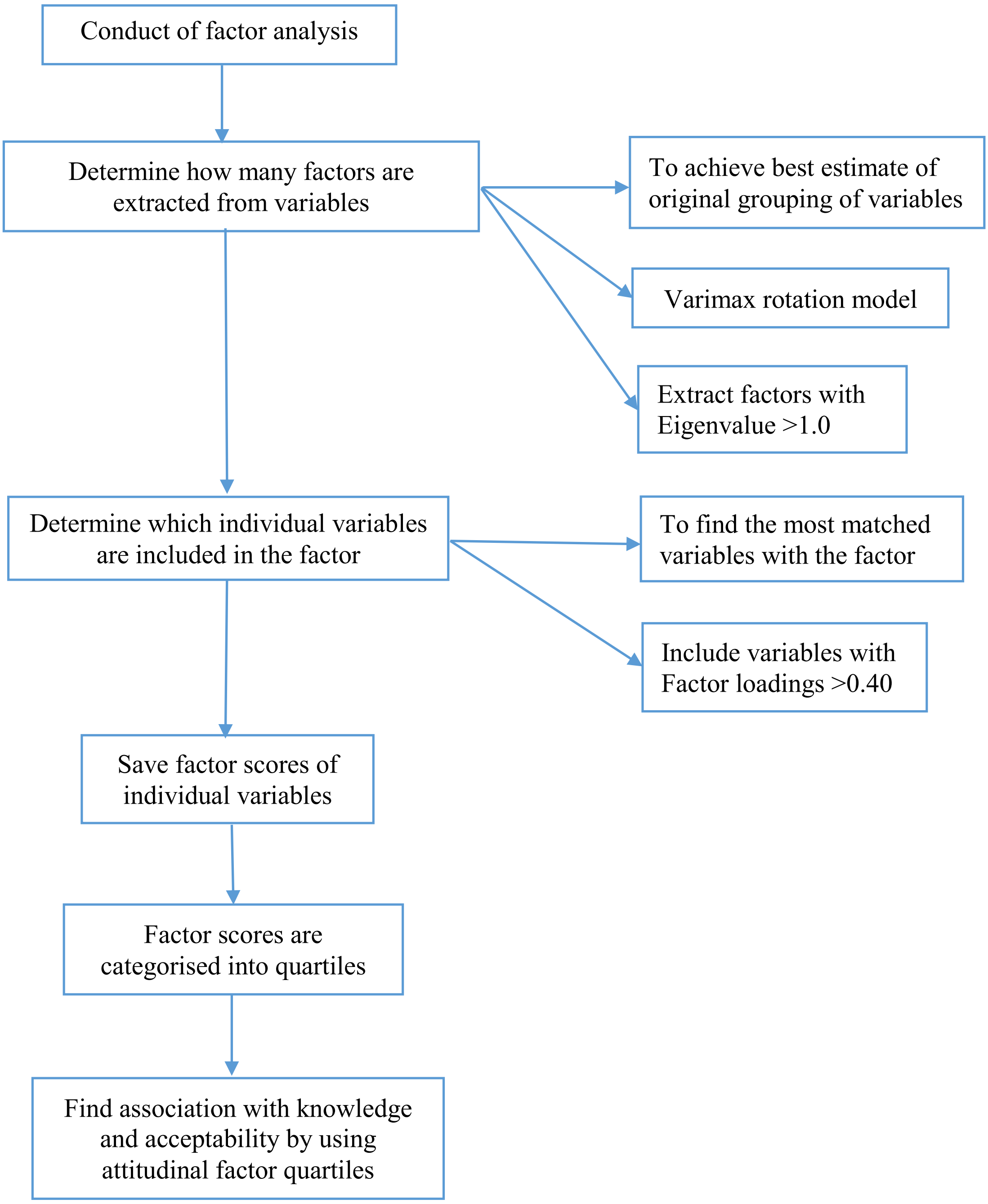
n46 where do you live?{urban,rural} 1.city 2.countryside

n47 which school are you studying?{highschool} 1.No. 1 school 2. No.2 school 3..No.3 school 4.Ning'an school 5.Hailin school

New/0

id Integer: 0-9 allowed Length: 4

Figure 3-11: Flow diagram of conduct of factor analysis



4 Chapter 4 HPV and cervical screening survey: Results

Chapter 3 described the methodology of my survey in Heilongjiang in China: in this chapter I present the results of that work.. I carried out a questionnaire-based survey and I report results based on summary data and analysis of the responses to each question in the questionnaire.

The first question in the questionnaire was a screening question about HPV awareness, which served to identify participants who had heard of HPV, and those who had not. The participants were subsequently divided into two groups based on the response to that screening question: 1) those who had heard of HPV were requested to answer all three sections in the questionnaire: i.e. the knowledge, attitude, and background questions; 2) those who had not heard of HPV were requested to answer the last two sections: only the attitude and background questions. Hence, when it comes to the analysis, description of characteristics of participants, awareness, attitude and acceptability, and association between these variables are shown among all the respondents; description of knowledge level and the association of knowledge level with other variables are only provided for respondents who had heard of HPV. The number of participants for any individual result is presented on the top line of each table of results.

Firstly, respondents' characteristics are presented as numbers and percentages. Secondly, results of chi-square testing undertaken to identify any initial differences in awareness, knowledge, attitudes, and acceptability between urban and rural participants, males and females, and <18 and >=18 participants are presented. Thirdly, results of logistic regression are presented. Logistic regression was undertaken under the following circumstances: a. when a difference was required to be identified between two specific categories of variables that had more than two categories; b. when there was confounding of the association between variables, and adjustment was required. Tables of results for the chi-square testing are not all presented because of the further regression analysis between the same variables (details are provided in the chapter).

4.1 Characteristics of participants

In total, 67 classes from five high schools in Heilongjiang province were approached. Within these five schools, 24 classes were from Grade 10, 23 classes from Grade 11, and 20 classes from Grade 12. The number of questionnaires distributed and returned in each school is provided in Table 4-1. No students asked to leave the classroom before the survey started. Students who declined to participate after they had read the questionnaire did not return the questionnaires. A total of 4,050 questionnaires were distributed, and 3,788 were returned. The overall response rate was 94.2%.

The characteristics of the participants are presented in Table 4-2. Participants were aged between 14 and 22 years and 16–19-year-old students accounted for the majority: 3,460 (91.3%). Over half were female: 2,060 (54.4%). A total of 740 (19.5%) participants were from rural areas and the remainder were from urban regions. Participants were equally distributed among the chosen five schools (approximately 20% from each school). Most of the students never smoked: 3,200 (84.5%) and 84 (2.2%) smoked every day.

Some differences in age, gender, and rurality were found among questionnaire respondents (Table 4-3). More rural participants than urban participants were aged 18 years or older. Gender and age were found to be associated with smoking through chi-square testing, and multivariate logistic regression further identified that males (22.5%) were more likely to have smoked than females (7.4%); participants who were aged 18 years or older were more likely to smoke than those younger than 18 years. Age and gender of respondents were also found to be associated with participants' schools. Hence, adjustments for age, gender, rurality, smoking, and school were needed when further analysis was undertaken because of the association between them. Tables 4-3 and 4-4 present these results of chi-square testing and logistic regression.

4.2 Awareness of HPV

Of all the participants (3,788), 499 (13.2%) reported that they were aware of HPV, meaning these students answered 'Yes' to the screening question 'Have you heard of HPV?' (Page 1 of the questionnaire). As discussed in Chapter 3, it was important to identify the students who were already aware of HPV: these students answered the knowledge questions in the questionnaire. They also answered the attitude questions, and comparisons are made later in this chapter between those who were aware of HPV and those who were not.

4.3 Knowledge of HPV and vaccination

A total of 499 (13.2%) participants had heard of HPV, and only these respondents answered the subsequent knowledge questions. The level of knowledge of HPV infection and vaccination among these participants is presented in Table 4-5 and missing data is also presented. Figure 4-1 presents knowledge levels in descending order in terms of the proportion of correct responses.

I divided the levels of knowledge into three groups. If less than one third of respondents reported having knowledge of a given area it was viewed as a low-level of knowledge; between one-third and two-thirds was viewed as a moderate level; over two thirds was viewed as a high level. Details are presented in Figure 4-1.

The high-level knowledge areas

- 'HPV vaccination is not 100% effective against cervical cancer' (n=366, 73.3%)
- 'Cervical screening is still necessary after HPV vaccination' (n=351, 70.3%)
- The risk of multiple sexual partners for cervical cancer (n=343, 68.7%)
- The asymptomatic nature of HPV infection (n=342, 68.5%)

The moderate-level knowledge areas

- 'HPV infection may cause cervical cancer' (n=327, 65.5%)
- The sexually transmitted nature of HPV infection (n=290, 58.1%)
- The condom role in the protection of HPV infection (n=199, 39.9%)

The low-level knowledge areas

- 'Most HPV can be cleared without treatment' (n=116, 23.2%)
- 'Poor personal hygiene can increase the risk of getting HPV' (n=30, 6.0%)

These results constituted a high-level overview of knowledge levels among participants who had heard of HPV (499, 13.2%). Knowledge level was also examined by overall scores for correct responses among these participants. As discussed in Chapter 3, participants were divided into two groups: 222 (44.5%) participants had a high level of knowledge and 255 (51.1%) had a low level of knowledge (22 participants missed answering some knowledge questions). Considering the multiple testing issues, high and low levels of knowledge among participants were used later in this chapter to identify the association with acceptability and attitudes instead of the level of knowledge of each question by participants.

4.4 Attitudes toward HPV and vaccination

The attitudes questions were categorised into six categories based on the Health Belief Model. These categories were perceived risk, perceived severity, perceived benefits, perceived barriers, other influences, and attitudes on stigma. Table 4-6 presents the attitudes towards HPV and vaccination among all the participants (n=3,788), i.e. including both those who had heard of HPV and those who had not. Questions related to the following issues were required to be answered only by females (2,060, 54.4%): personal perceived risk of cervical cancer, personal perceived impact of cervical cancer, personal perceived necessity of taking up cervical screening, and the recommended frequency of cervical screening. Males who answered these questions were excluded from the analysis.

4.4.1 Overview of attitudes

Areas of attitudes towards HPV vaccination were listed under headings according to Health Belief Model concepts. Response options of somewhat/strongly agree and somewhat/very likely in the questionnaire were combined together respectively to obtain an overview of attitudes among participants.

Perceived risk of HPV infection, and cervical cancer

Regarding the question ‘How likely the risk is that you will get HPV infection in the future?’, 325 (8.6%) participants perceived their personal risk of HPV (those who chose somewhat likely and very likely options); for question ‘How likely the risk is that you will get cervical cancer in the future?’ 151 female participants (7.3%) perceived their personal risk of cervical cancer (somewhat and very likely).

Perceived severity of HPV infection and cervical cancer

Regarding the statements ‘HPV infection would be disruptive to my physical health/social life/sexual relationships’ over half of the participants agreed (strongly and somewhat agreed) with all these statements. For statements ‘Cervical cancer would be disruptive to my physical health/social life/sexual relationships’, over half of female participants agreed (strongly and somewhat agreed) with these. Data is presented by number and percentage.

- The most worrying impact of HPV infection (n=2,721, 71.8%) and cervical cancer (n=1,674, 80%) was that on physical health
- The second most worrying was the impact on sexual relationships by HPV infection (n=2,374, 62.7%), and by cervical cancer (n=1,285, 62.4%)

- The least worrying was the impact of HPV infection (n=2,091, 55.2%) and cervical cancer (n=1,182, 57.4%) on their social life.

Perceived benefits of HPV vaccine

A total of 2,968 (78.4%) participants believed the HPV vaccine could protect them from HPV infection, while 2,414 (63.7%) believed the vaccine could prevent cervical cancer. Only 542 (14.3%) participants agreed with the statement that the HPV vaccine would lead to people having more sexual partners. Regarding female participants, 1,684 (81.7%) knew it was still necessary to be screened after vaccination, and 548 (26.6%) agreed with the statement that the frequency of screening could be reduced after vaccination.

Perceived barriers of HPV vaccine

Regarding the statements 'I am concerned that HPV vaccines have not been proved to be effective in preventing cervical cancer', 'I am concerned that HPV vaccines may have minor side effects such as fatigue or fever', 'I am concerned that HPV vaccines may have major side effects such as long term illness', 'I am worried that HPV vaccine costs too much', and 'I trusted companies that make HPV vaccines', participants presented the barriers (strongly/somewhat agreed with the statements) to HPV vaccines. The findings are described in descending order below.

- The first barrier (n=2,707, 71.5%) was minor side effects such as fatigue or fever
- The second barrier was the effectiveness of the HPV vaccine not having been proved (n=2,001, 52.8%)
- Less than half of the participants worried about the cost of the vaccine (n=1698, 44.8%) and the major side effects of the vaccine (n=1,689, 44.6%).
- 1,295 respondents (26.5%) did not trust the companies that produce the HPV vaccine.

Other influences on the acceptability of HPV vaccine

Regarding the statements 'I would be vaccinated if my friends/parents/doctors/school/public service ads recommend me to', participants revealed whether they would be influenced by others (strongly/somewhat agreed with the statements)

- The recommendation participants would be most likely to take was that of their parents (n=2,503, 66.1%).
- Doctors and nurses' recommendations ranked in second place (n=2,302, 60.7%).
- 1,746 respondents (46.1%) would take a school requirement into account when deciding whether to be vaccinated against HPV

- 1,473 respondents (38.9%) would be likely to take their friends' recommendations.
- 1,017 respondents (26.9%) would be influenced by public service health advertisements.

Attitudes on the stigma of HPV infection

Regarding the statements on stigma associated with HPV infection (Table 4-6), I found the most commonly identified stigma was 'if someone has HPV, people will gossip' (n=1,911, 50.5%), followed by 'people will keep a social distance' (n=1.363, 40%), 'people would think the person is promiscuous' (n=1,118, 29.5%). 643 respondents (17%) agreed with the statement that people who are infected with HPV are likely to have been infected as a result of them or their partners being unfaithful.

4.4.2 Respondents' uncertainty in attitudes towards the HPV vaccine

A significant proportion of respondents were unsure whether they should accept the HPV vaccine in terms of the benefits, barriers, stigma, and other people's opinions (Table 4-6).

20–30% of the participants chose 'Unsure' option for the following statements

- The worry of impact on sexual relationships by HPV infection (n=806, 21.3%) and by cervical cancer (n=472, 22.9%)
- The effectiveness of the HPV vaccine (n=1049, 27.7%)
- The major side effects of the HPV vaccine (n=1010, 26.7%)
- The stigma of HPV infection in promiscuity (n=895, 23.6%), unfaithfulness (n=1070, 28.2%), and social distance (n=830, 21.9%)
- The recommendation from parents (n=774, 20.4%) and doctors (n=887, 23.4%) in terms of getting vaccinated

30–40% of participants chose 'Unsure' option on if they should take the recommendation of

- School (n=1130, 29.8%)
- Friends (n=1322, 34.9%)
- Public service health information advertisements (n=1313, 34.7%)

Nearly 40% of participants were unsure if they should trust the drug companies (n=1479, 39%).

4.4.3 Summary of results of attitudes

All the respondents (n=3,788) were requested to answer the attitude questions, including both those who had heard of HPV and those who had not, but missing data was found as well (the numbers depended on the question). These results were used to identify the association between acceptability of the vaccine and level of knowledge, reported later in this chapter.

4.5 Differences by age, gender, and rurality

Differences in the awareness of HPV infection, knowledge of and attitudes towards HPV infection and vaccination, and acceptability of the HPV vaccine by age, gender, and rurality were initially explored by chi-square testing (Tables 4-7, 4-8 and 4-9). Further exploration was made by logistic regression in the areas of knowledge and attitude in those areas where differences were found (Tables 4-7, 4-8 and 4-9). In order to avoid insufficient statistic power caused by the very few responses in each of the categories when making comparisons, I combined attitude responses into three options 'Disagree', 'Agree', and 'Unsure'. The influence of smoking was also examined.

4.5.1 Awareness of HPV

Regression analysis was performed to identify the influence of age, gender, and rurality on the awareness of HPV (Table 4-9). Differences in terms of rurality were found between people who had heard of HPV and those who had not: students from rural areas had lower awareness (4.5%) of HPV than those from urban areas (15.3%) (OR=0.33, 95% CI=0.22-0.49, $P<0.001$). No differences of age and gender were found in the awareness of HPV ($P=0.411$).

Among participants who smoked every day (n= 20, 23.8%) (OR=2.09, 95% CI=1.25-3.49, $P=0.005$) and those who used to smoke and had given up (n= 21, 23.6%) (OR=2.17, 95% CI=1.27-3.68, $P=0.004$) were more likely to have heard of HPV compared to those who had never smoked (n = 404, 12.6%). (Table 4-9).

4.5.2 Knowledge of HPV infection and vaccination

Regression analysis was carried out and differences in gender and rurality were found in one area of knowledge of HPV and vaccination. The comparisons were made between those who reported knowing about HPV, and those who did not. (Table 4-7 and Figures 4-2).

More males than females, and more rural than urban participants knew

- 'Condom use lowers the risk of HPV infection' (49% vs. 32.7%), (60.6% vs. 39.3%)

Smoking was not found to be associated with knowledge levels (Table 4-9).

4.5.3 Attitudes towards HPV infection and vaccination

Regression analysis was made using the reference group 'Disagree' in the areas of attitude in which differences were found by chi-square testing. Differences according to gender were found in the following areas of attitude below (Table 4-8).

More females than males

- Perceived the physical health impact of HPV infection (74.2% vs. 69.6%)
- Were concerned about the effectiveness of HPV vaccines (53.8% vs. 52.7%)
- Worried about the HPV vaccine's minor side effects (73.5% vs. 69.3%)
- Would be influenced by their parents (67.7% vs. 64.3%)

More males than females

- Believed the HPV vaccine would lead to people having more sexual partners (21.7% vs. 8.8%)
- Worried about the cost of the vaccine (48.9% vs. 41.7%)
- Trusted the drug companies (38.9% vs. 30.6%)
- Would be influenced by friends and TV advertisements.

To summarise, females were more likely to understand the potential health implications of HPV infection, worry about the side effects of HPV vaccines, and be influenced by parents. Males were more concerned with the cost of the vaccine, the vaccine leading to people having more sexual partners and be influenced by friends and TV advertisements.

No significant differences in attitudes towards HPV infection and vaccination were found by rurality and age. There were not significant differences in attitudes towards stigma about HPV infection by age, gender and rurality.

4.5.4 Acceptability of the HPV vaccine

The general acceptability (those who are likely to accept the HPV vaccine) was 68% among all the participants, including both those who had heard of HPV and those who had not.

In terms of demographics, differences in gender were found in the acceptability of HPV vaccines. More females (n= 1431, 69.5%) than males (n=1110, 66.3%) were likely to accept the HPV vaccine (OR=1.69, 95%CI=1.38-2.07, P<0.001). No differences in age or rurality were identified in the acceptability of HPV vaccine.

The acceptability of HPV vaccines was not found to be different between participants who had heard of HPV and those who had not. There was no association between smoking and acceptability (Table 4-9).

4.6 Predictors for the acceptability, awareness, and knowledge of HPV

4.6.1 Factor analysis results

The result of *Bartlett's Test* (*P*<0.001) confirmed the assumption that the 20 attitude variables had some correlations between them. Therefore, it is appropriate to use factor analysis to explore these further.

First, five factors had an *eigenvalue* greater than 1.0 (determining the number of factors to be retained) and were derived from the analysis. The cumulative variance explained by these five factors was 60.07%. Second, variables that had more than 0.40 loadings under the specific factor were included in this extracted factor (Table 4-10).

Two items were excluded for the following reasons (data is not shown in the table).

- The item 'Having an HPV vaccination may lead to people having more sexual partners as they think their risk of disease is reduced' was excluded because its loadings under the five factors were all less than 0.40 and thus it could not be explained by the five factors.
- The item 'I trust the company that make HPV vaccines' was excluded. Because it could not be categorised and explained by any factors, although its loading for factor 1 was 0.58 (greater than 0.40).

The remaining variables were categorised into five factors (Table 4-10).

- Factor 1 (Items 1–5): named other influences, explained 29.68% of the total variance.
- Factor 2 (Items 6–9): named stigma, explained 10.24% of the total variance.
- Factor 3 (Items 10–13): named perceived barriers, explained 7.32% of the total variance.
- Factor 4 (Items 14–16): named perceived severity, explained 7.13% of the total variance.
- Factor 5 (Items 17–18): named perceived benefits, explained 5.70% of the total variance.

The factor score for each attitudinal factor was calculated by summing the frequencies of the option in the responses weighted by their factor loadings. Factor scores were based on the participants' rating of responses to the respective factors, and higher scores reflect a higher rating of responses to a given factor. Factor scores were saved in SPSS and were not displayed in the analysis. In order to clearly understand the rating, I first translated the rating of responses into this order in SPSS: Unsure, Strongly disagree, Somewhat disagree, Somewhat agree, Strongly agree. Hence, higher rating meant 'Somewhat agree' and 'Strongly agree'. Then, I used quartiles to categorise the five factors' scores. These quartiles were used as independent variables in the logistic regression. The lowest quartile was my reference group, which was close to 'Unsure' and 'Strongly disagree' responses and highest quartiles, level 4, close to 'Somewhat agree' and 'Strongly agree' options.

4.6.2 Predictors for the acceptability of HPV vaccines

Based on the data analysis, four positive predictors of the acceptability of HPV vaccines were found. The higher factor scores participants had, the more likely it was that they would be influenced by others, perceive the severity of HPV, perceive the benefits of HPV vaccines, etc. (Tables 4-11). No negative positive predictors were found.

- Other influences on the acceptability of HPV vaccines (positive): Compared to the participants who were not likely to accept HPV vaccines, those who were likely to be vaccinated would be more influenced by other people, such as friends, parents, and doctors (OR=3.89, 95%CI=2.75-5.49, P<0.001).
- Perceived severity of HPV infection and cervical cancer (positive): Participants who were likely to accept HPV vaccine were more likely perceive HPV infection as a serious issue (OR: 2.53, 95% CI: 1.87-3.42, P=0.002).
- Perceived benefits of the HPV vaccine (positive): Participants who were likely to be vaccinated were more likely perceive HPV infection as beneficial (OR: 1.54, 95% CI: 1.17-2.03, P=0.002).
- High level of knowledge of HPV infection and vaccination (positive): Participants who were likely to be vaccinated were more likely to have a high level of knowledge. (OR: 2.43, 95% CI: 1.39-4.25, P=0.002)

4.6.3 Predictors for the awareness of HPV

One positive predictor was found for the awareness of HPV (Table 4-11).

- Other influences (positive): Participants who had heard of HPV were more likely to be influenced by others on the acceptability of HPV vaccines (OR=1.66, 95%CI=1.24-2.20, P=0.001).

4.6.4 Predictors for the knowledge of HPV and vaccination

High and low levels of knowledge were used to make comparisons in terms of age, gender, rurality, and smoking. No differences were found (Table 4-11). One negative and one positive predictor of knowledge level were found: attitudes on stigma and the perceived severity of HPV (Table 4-11).

- Stigma about HPV-infected people (negative): participants who had a high level of knowledge of HPV and cervical cancer were less likely to have stigmatising attitudes towards HPV infection (e.g. People would gossip about those who had the HPV infection) (OR: 0.48, 95% CI: 0.27-0.84, P=0.011).
- Perceived severity of HPV infection (positive): participants with a high level of knowledge of HPV and cervical cancer were more likely to perceive the severity of HPV infection (e.g. HPV infection would be disruptive to my physical health) (OR: 2.91, 95%CI: 1.66-5.13, P<0.001).

4.7 Summary of results

4.7.1 Key findings

Awareness and knowledge of HPV and vaccination

An overall low level of awareness of HPV (13.1%) was found. However, among those who did report knowing about HPV, low, moderate to high levels of knowledge were identified among participants for individual knowledge items.

Attitudes towards HPV infection and vaccines

Over two thirds of participants worried about the health impacts of HPV infection and cervical cancer, but the perceived personal risk of HPV infection, and of cervical cancer was low (8.6% in all the respondents and 7.3% in females respectively)

Approximately two thirds of participants believed the HPV vaccines to be effective in preventing cervical cancer. A high proportion of female participants (81.7%) were aware of the need for cervical screening after vaccination.

The most commonly reported barrier (over two thirds of respondents) to HPV vaccine was concern about side effects (many of them minor). Less than half of the participants worried about the cost of the vaccine. Students were most likely to accept the recommendation of their parents about whether or not to accept the vaccine (66.1%). The most identified stigma relating to HPV infection was 'if someone has HPV infection, people will gossip' (50.5%).

High levels of acceptability (63.2-80.6%) for the HPV vaccine were found irrespective of the age, gender, and rurality of participants, or their levels of awareness and knowledge of HPV infection and vaccination.

Differences by in age, gender, and rurality

Differences in response were found by age, gender, and depending on rural or urban location of the student. Rural participants had lower awareness, and females were more likely to be willing to accept the vaccine if it were to be available. Differences in terms of gender existed in knowledge levels and attitudes, but no pattern was found, and whether males or females had more knowledge or were more likely to perceive barriers or be influenced by others depended on the specific topic.

Predictors for acceptability and knowledge of HPV vaccines

The significant positive predictors for acceptability were the influence of others, perceived severity of HPV infection, perceived benefits of the HPV vaccine, and the level of knowledge. This meant that the more participants were influenced by others, the greater they perceived the severity of HPV infection and the benefits of the vaccine to be, and the higher their level of knowledge, the more likely they were to accept the HPV vaccine. No significant negative predictor was found.

The significant positive predictor of knowledge was perceived severity. The significant negative one was attitudes on stigma.

4.7.2 Interpretation of results

Missing data

There was missing data in the question responses. The proportion of missing data was less than 2% in each question relating to knowledge, background, and attitude to stigma, and less than 1% in the other attitude questions. The structure and format of the questionnaire may have contributed to this difference in the proportion of missing data (Appendices 4 and 5). As the questionnaire was printed double-sided, and Pages 2 and 3 (including most of the attitude questions, but not those relating to stigma) were inside, Pages 1 and 4 (including the questions on knowledge, background, and stigma) may have appeared to the participants to be the covers of the questionnaire. Hence, some participants might have failed to answer the questions on the 'cover'.

No missing data was found in three variables— whether rural or urban, awareness of HPV, and name of high school. First, regarding whether rural or urban (the first issue mentioned), I explained this item a few times prior to students filling in the questionnaires in case that they did not understand which regions should be defined as urban and which ones as rural. As soon as I made this point, the students probably all filled in the question as I indicated. Second, question about HPV awareness was the first in the questionnaire. All the students were required to answer it as they had to find out which of the subsequent parts they should fill in next. Third, the school name was marked in all the questionnaires once they were collected from each school; hence, no missing data was found here.

Demographics of participants

<u>The oldest and youngest participants</u>: Students usually go to school at 6 or 7 years old, and high school education starts from Grade 10 to Grade 12. So, high school students aged 16–19 years old were the potential recipients of my survey. Given that students from rural regions usually go to school one to three years later than students from urban areas, older participants were mostly found in rural regions, and it was not unexpected that some participants were older than 19 years. Two of the participants were 14, which may have been because of personal or family reasons. But as expected, most participating students (91.3%) were aged between 16 to 19 years old at the time of the survey.

<u>The proportion of participants from rural regions</u>: As three of the high schools are located in the urban regions of Mudanjiang city and they only recruit students from among the residents of the city, no rural students attend these schools. The other two schools have almost the equal number of urban and rural students. Hence, approximately 20% of the participants in my survey were rural students.

The awareness of HPV and the acceptability of the HPV vaccine

The low level of awareness of HPV is not surprising in terms of the study location (Mudanjiang city in North China), the lack of sexual health education in high school, and the young ages of some the participants—it is likely that few respondents would be sexually active.

It is difficult to interpret the high acceptability of the HPV vaccine irrespective of demographics, socio-economic conditions, health care, and educational factors. But it might be helpful to consider why willingness to take up the HPV vaccination is higher in this Chinese population than among people in other countries where the HPV vaccine has been introduced and promotion programmes have started. Some reasons below might explain the hypothetical high acceptability of the HPV vaccine.

Lack of detailed thought: The low level of awareness and perceived risk (less than 10% for HPV infection) suggested even though they did not know what HPV was or whether they were at risk, they were still willing to be vaccinated. This might because they have not thought hard about this choice.

Prevention of the serious disease of cancer: Cancer is a serious disease and may lead to death in a short period, even when treated properly. The fact that cervical cancer can be prevented by the vaccine might give people a hope to prevent this cancer. Moreover, the high level of perceived severity of HPV infection and of cervical cancer may partly explain the high acceptability of the HPV vaccine in that it is needed to prevent a disease that would generate a serious health impact in the future.

Only a few hypothetical scenarios were presented: I have not created several hypothetical scenarios of acceptability in terms of a varied level of cost. One reason for this is that I am not sure which factor (i.e. cost or side effects) is ranked highest among Chinese teenagers' perceived barriers to the HPV vaccine. Furthermore, it is not possible to list all the potential barriers under the question of 'How likely would you be to accept the HPV vaccine?', as too many choices might lead to weaker statistical power and more bias. Hence, the perceived barriers were examined independently and later added to the analysis of predictors of acceptability of HPV vaccine to see their influence.

Knowledge of HPV infection and cervical cancer

Influence of traditional Chinese culture

Nearly three-quarters of my participants understood that the HPV vaccination was not 100% effective and that cervical screening was still necessary after vaccination. Zhao's study [201], carried out in mainland China in 2012, reported that 4.5%–10.8% of 15–19-year-old women had experienced sexual activity. Further, it is estimated that less than 10% of female students would have the opportunity to get cervical screening, and those who finally received screening would be much less. This suggested that most teenagers in China would not know what cervical screening was. Possible reasons for this unexpectedly high level of knowledge are presented below.

The conservative attitude of Chinese people: Chinese people tend to think neutrally and conservatively. Participants might think that any kind of vaccination is not absolutely effective and that even people who got the vaccine might still have a chance of suffering from the illness. Moreover, as a result of the vaccinations participants have already received (e.g. hepatitis B), they may know that very few vaccinations provide lifelong immunity for human bodies. That cervical cancer could be prevented by vaccination is a new concept, and it will take time to prove its effectiveness and for people to believe it. Hence, suspicion might exist amongst adults as well as teenagers.

The influence of Chinese social norms: China has a long history of the feudal system, resulting in the deeply rooted social perspective that people, especially women, are not supposed to have more than one sexual partner or initiate sexual activity prior to marriage. Thus, having multiple sexual partners and engaging in sexual activity at an early age may be viewed as going against social norms. Moreover, the question 'Having multiple sexual partners increases the chance of getting cervical cancer' seems like a negative statement, and would lead participants give answers that were correct in terms of social and moral standards, though I tried my best to make the question look more neutral and less challenging to Chinese social norms.

Areas of lower knowledge

A small proportion of respondents (less than 10%) correctly answered the knowledge question that 'Poor personal hygiene can increase the risk of getting the HPV infection' is false. This may because the statement seems common sense that personal hygiene would affect the risk of people getting any disease, regardless of the kind of infection, such as hepatitis B and some respiratory infections. However, sexually transmitted infection differs from other infections, which would not be infected through sharing toilet or be protected by good habits of hand-washing. Hence, sexual health education is suggested.

The self-healing feature of the HPV infection, a more specialised but necessary knowledge item, was known by approximately one quarter of participants. This suggested that some specialised sexual health education is needed in the future, to both increase self-protection and reduce anxiety among people.

Approximately one third of the participants knew that condoms could be used for the prevention of sexually transmitted diseases. A higher level of knowledge could have expected. HIV health education and promotion programmes are very common in China among high school and college students, and one of the most repeatedly emphasised aspects of the programme is the role of condoms in the prevention of sexually transmitted disease. 58.1% of the participants knew that HPV could be sexually transmitted, but only one third of them were aware of the use of condoms in preventing this. This suggested students might lack real understanding of preventive knowledge in terms of sexually transmitted infections.

Incorrect responses

Two knowledge statements were incorrectly answered by over 70% of participants. These were: 'HPV vaccination is 100% effective against cervical cancer' and 'Regular cervical screening is not necessary after HPV vaccination'. The correct answer for both questions was 'False'. The conservative attitude of Chinese people discussed earlier in this chapter might explain the incorrect responses to these two items.

Uncertainties in interpreting the results

<u>The appropriate recipient of the HPV vaccine</u>: Two-fifths the participants knew that HPV vaccine targeted people who were not sexually active. This result was unexpected, as no HPV vaccine promotion campaign is available in China to inform the public of whom the HPV vaccine targets, when the best time for vaccination, etc is. Therefore, I have reservations about this result.

<u>The asymptomatic feature of the HPV infection</u>: Over two thirds of participants knew that HPV infection was asymptomatic. This revealed a higher level of knowledge among participants even than 'the sexually transmitted nature of HPV infection' (58.1%) and 'HPV infection may cause cervical cancer' (65.5%). I have reservations about the validity of this result.

Attitudes towards HPV, cervical cancer, and vaccination

Low level of perceived risk of HPV and cervical cancer

Below are the probable reasons for the low levels of perceived risk.

Lack of sexual experience among young teenagers: Few Chinese high school students have sexual experience (4.5–10.8% [60]; the percentage is close to the percentage of perceived risk) and they would, thus, not have a clear understanding of the likelihood of getting the HPV infection through sexual activity.

Lack of ability to translate the knowledge into estimating the risk of HPV infection: Nearly half of the students already knew that HPV was a common sexually transmitted infection, but had not realised the risk. Knowing a fact is one thing; applying that knowledge to estimate susceptibility to HPV infection, or the relationship between HPV infection and potentially developing cervical cancer is another. Many factors are involved in the process of estimation, e.g. the confidence in their health, the understanding of the risky sexual behaviours, etc.

Furthermore, the mature health care system in urban regions may make participants (80% of participants are urban students) less likely to realise the risk. Further, occurrence of cervical cancer in adults may further reduce the risk that young teenagers would perceive.

Perceived barriers to the HPV vaccine

As expected, the effectiveness and safety of the HPV vaccine were the most commonly reported barriers. Cost was not the biggest barrier for the young Chinese teenagers. This may be because such teenagers have not started to earn their own money and thus have not had the opportunity to make decisions concerning whether they need to pay and how much they would pay. Thus, their views may not be treated seriously in terms of payment for the vaccine. But their attitudes, to some extent, might play a role in the decision-making of their parents.

Trust in drug companies is another reported barrier. One third of the participants reported low trust in drug companies, and even more (39%) were unsure (chose ‘Unsure’ option in the responses) about them. The weakness of the question is that it did not state whether the drug company was an external (i.e. international) one or an internal (Chinese) company. Participants might have given very different answers to the question if this were clarified, as the Chinese people tend to have much more faith in Western pharmaceutical companies in terms of technology and quality of production.

Other influences on the acceptability of the HPV vaccine

Young teenagers (two-thirds in my survey) chose parents as the most trustworthy source of information for advice concerning whether to get or not to get HPV vaccination, and the opinions of doctors ranked in second place. Young teenagers relied more on their parents for decision-making; this may because they were largely dependent on their parents financially and educationally, and trust their care for them.

Attitudes on stigma of HPV infection

Chinese people tended to have a low level of awareness of the need to protect privacy in public spaces, which might partly be because of the lack of facilities for personal space caused by a large population base and poverty. Hence, it is easier for people to find out private information about others. Moreover, sexually transmitted infections may not be well understood in China, and people might gossip. My survey, nevertheless, found that the stigma surrounding HPV infection was not huge (less than half participants reported stigma associated with HPV infection), and this may suggest that the increasing openness in China is leading to a reduction in stigmatising attitudes towards people with sexually transmitted infections. This may be partly attributed to the efforts that have been made nation-wide increasing awareness of HIV infection, and treating AIDS patients in a humane way. However, the stigma may have been underestimated as a result of the lack of awareness of the HPV infection among participants; my study did not examine this possibility.

The weakness in these questions was that I did not clarify whether other people in their social group were knowledgeable about the HPV infection. Therefore it is difficult to predict whether an increase in people's knowledge about the disease would lead to an increase in psychological pressure in social situations for those infected with HPV.

Predictors for acceptability and knowledge level

Predictors derived from factor analysis highlighted the three main concepts of the Health Belief Model: perceived severity of HPV infection, perceived effectiveness (benefits) of the

HPV vaccine, and perceived barriers to the HPV vaccine. Another two predictors were other influences on accepting the HPV vaccine, and stigmatising attitudes on HPV infection.

In deciding whether to accept the HPV vaccine, young teenagers would be influenced by their parents and doctors, the perceived severity of HPV infection and of cervical cancer, as well as the perceived benefits of the HPV vaccine. The results suggested that they would be more likely to get vaccinated if they knew that HPV infection and cervical cancer had a negative impact on their health and that the HPV vaccine was effective. In terms of knowledge level, a possible explanation is that the more they knew about HPV infection, cervical cancer, and the HPV vaccine, the more likely it was that they would know about the perceived severity and benefits, and in turn the more likely they would be to accept the HPV vaccine.

Differences in knowledge and attitude by age, rurality and gender

Differences between the knowledge of rural and urban participants was found with regard to protective role of condoms for HPV infection. However, because the knowledge questions were answered only by participants who had heard of HPV, only a small number of rural students (around 35) had heard of HPV, and fewer than 5 rural students gave certain response option (eg true, false, or unsure), statistic power could not be achieved with such an insufficient sample size. For example, difference in knowledge by rurality found in the area of condom role and surprisingly rural participants presented higher knowledge level. The big range of 95% confidence interval (1.41-7.04) for this odds ratio (odds of rural participants'' knowledge in contrast to urban participants') indicates the limitation in the reliability of the result. Further, the unbalanced proportion rate between rural and urban participants limits the generalisability of the results. Differences in rurality need to be reassessed by studies with a better-balanced distribution of urban and rural participants. No difference by rurality was found in terms of attitudes.

Gender-based differences in the knowledge of HPV and vaccination depended on the specific topic. No conclusion can be easily drawn that whether one gender had more knowledge overall than the other. Regarding attitudes, male students were more concerned with the vaccine's cost and its potential impact on number of sexual partners. In contrast, female students cared more about the potential health impact of the vaccine and its side effects. Parents, doctors, and schools all played important roles in the acceptance of HPV vaccines, and females expressed more dependence on their parents' views, while males reported greater reliance on their friends' views. These results provided useful information on what needs to be included and emphasised in future HPV vaccination campaigns.

No differences were found in areas of knowledge and attitudes by age.

4.7.3 Methodological issues and comparison with other studies

Sampling

Selection bias

One-province study: It was not a multi-centre study, which may compromise the generalisability of the sample to wider population in China. The interpretation of results needs to be cautious due to the specific geographical location—the most northeastern province in China, ranked in the middle of China in terms of economy and population. My findings may reflect the teenagers' perceptions in some middle-developed inland provinces.

Nevertheless, they may not be applicable to the following regions:

- Four municipalities
- Eastern coastal provinces
- Five autonomous regions (education and health care resources are relatively limited)

Study of only one age group (teenagers): My study did not investigate all population groups who would be involved in introduction of the HPV vaccine in China, for example young adults (18-26 year old, the likely population in college), parents, and health professionals. However, it does provide among the first evidence from Chinese teenagers—the majority of the potential recipients—whose views are poorly understood to date. Teenagers in my survey expressed worries about the side effects, concerns about potential increased sexual behaviour following HPV vaccination, and their susceptibility to cervical cancer, etc. Existing data on mainland Chinese teenagers is limited, and few conclusions can be drawn. One reason for this lack of published data reporting the knowledge and attitudes of Chines teenagers might be uncertainty regarding how much influence the views of teenagers would actually have on the introduction of the HPV vaccination in the country.

'Good' student perspective: My study used a convenience sampling method, which included participants who are among the top 60–75% of students in the city, and provided views from the perspective of a 'good' student. The participants—'good' students preparing themselves for future studies at university, may be over-represented, and my findings may not represent about the views of less able students. However, of the groups engaged in the vaccination programme, the ‘good’ high school students are the group most likely to influence their peers, exerting their influence through universities and schools.

No family background data (e.g. socio-economic factors): ‘Good’ students usually come from well-educated families, and their parents are more likely to have a strong economic capacity. But the exclusion of private, international, and vocational schools in the recruitment for the study would have helped to ensure a relatively balanced range of family backgrounds—neither excessively wealthy nor overly poor. No family background questions were asked in the questionnaire, because participants were too young to provide accurate family income information.

Sampling methods in other similar studies

Similar studies on the knowledge of and attitudes towards HPV vaccines have mostly been quantitative ones and questionnaire-based surveys [123, 124, 187, 201]. Some were interview or focus group studies [198, 209]. In terms of the population background, some studies were school-based [123, 209], some were hospital- or clinic-based [187, 201], and some were community-based [124, 198]. All of them were cross-sectional studies due to research priority, cost, and feasibility.

Response rate

Non-responders to the survey

The overall response rate was 94.2% (4,050 student were approached, and 3,788 questionnaires were returned). For ethical and logistical reasons, I was unable to access students who did not return the questionnaires and find out the characteristics of such students. However, given the small number of non-responders (5.8%) it is unlikely that even outlier responses from these non-participants would have influenced the overall results Moreover, I had anticipated a response rate of approximately 90%, and sample size calculations were based on this response rate.

Response rate in other similar studies

The high response rate might be related to the sampling method. A systematic review among European adolescents reported a high response rate for classroom-completed questionnaire surveys (86–100%), and a lower response rate for home-completed questionnaire surveys (21–79%)[190].

Quality of the instrument

Validity of the questionnaire

No internationally-validated questionnaires on knowledge of and attitudes towards HPV are available. The questionnaire in my survey was self-designed, based on both the Western and Chinese-language literature. The draft questionnaire was refined by cognitive interviews with 10 Chinese students aged 21–24 years old, based in Edinburgh. The cognitive interviews improved internal validity by measuring the comprehension of the questionnaire, refining the wording and the format. It helped me to examine whether the questionnaire measured what I really wanted it to and not something else. But it may also have reduced the external validity of the questionnaire, as it used teenager-friendly language, applied particularly to teenagers at public high schools in middle-developed provinces in China (assuming the potential participants had a traditional secondary education in China).

Moreover, there are challenges in choosing specific wording for some questions, as there may be no translation to convey exactly the same meaning in a different cultural and linguistic l setting. For example, the words “promiscuous”, and “gossip” have similar words in the Chinese language (see Appendix 5), but with differing degrees of positive and negative connotations (eg. still negative, but more neutral in Chinese than in English). Hence, issues in translation and culture need to be taken into account when the Chinese language findings are reported in English. . Yu and colleagues have highlighted common features of translating across cultural and language barriers, i.e. maintaining the original intent of the questionnaire, optimising the cultural relevance of the concepts, and comprehensibility of the translated questionnaire. They emphasise the importance of literal and cultural adaptation rather than simple word translation in maintaining equivalence of concepts. [234]

Health Belief Model

I used the Health Belief Model in the development of attitude questions. It has clear benefits in identifying behaviours such as emotional and psychological thinking, but it also has some recognised limitations. For example, the Health Belief Model does not sufficiently account for a person's attitudes, beliefs, or other individual determinants that dictate a person's acceptance of a health behavior. There is also concern that it does not take into account behaviors that are performed for non-health related reasons such as social acceptability, or sufficiently allow for environmental or economic factors that may prohibit or promote the recommended action. Critically for my survey, there are concerns that the Health Belief Model assumes that everyone has access to equal amounts of information on the illness or disease. There have also been concerns expressed about its use in traditional, non-Western populations [235].

To address these gaps, I added questions examining demographic factors, and stigma, and provided summary information about HPV in the questionnaire itself.

The Health Belief Model was developed in the Western setting, but it does have some utility in exploring attitudes among Chinese populations. The most detailed analysis of the applicability of the Health Belief Model in a Chinese population is that of Lai and Cheng who compared the variables benefits and barriers in the Health Belief Model among Hong Kong Chinese adults and adolescents in response to an imaginary flu outbreak and a hypothetical vaccine [236]. They concluded that the health belief model variables on prevention intention had some applicability for adolescents but less so for adults in their study populations.

Other researchers have also drawn on the Health Belief Model in studies exploring attitudes and understanding of a range of health behaviours among the Chinese population, both Mainland and Hong Kong. Some examples include: Lau et al examined acceptability of HPV vaccines and perceptions of HPV among men who have sex with men in Hong Kong [237]; Yue and colleagues found that the Health Belief Model was reliable in predicting medication adherence in an adult Chinese population [238]; Li and colleagues developed a survey questionnaire based on the Health Belief Model to examine factors associated with willingness for HIV testing among Chinese women [239].

Despite the limitations noted above, I am confident that use of the Health Belief Model was appropriate to inform the objective of my research, aiming to explore health understanding and attitudes that had not previously been systematically explored in the Chinese population. Nonetheless, it is important that future research draws on other theories of health behaviours to deepen understanding of factors influencing these attitudes and behaviours. There is also scope for a more detailed examination of the applicability of Health Belief Model constructs among young people in modern China.

Completeness of questionnaire

There were between none and 75 missing data items (0–2.0%) for different questions. The question on age had the highest level of non-response (75 non-responders). The question on participant gender, the questions of attitudes to stigma each had 52-53 non-responders. The other knowledge and attitude questions had no more than 35 non-responders. It is not feasible to have enough statistical power to analyse their characteristics because of the small number of non-responders. Thus, they were excluded from data analysis.

Data management

Data entry

I used Epidata for data entry, and it has clear benefits that prevent more errors from occurring.

- The layout of the database was operator-friendly—easy, straightforward, and highlighted coding areas.
- The format of the database looked exactly the same as the questionnaire on which the original data was collected. It minimised the potential complications in finding the exact field at each data entry.
- The double-check function in Epidata allowed me to set a limit for each field and restrict the database to accept only a few specific numbers for each variable. Immediate detection and correction of problems with data was carried out as data was entered. It substantially minimised the potential errors made during data entry, such as mistyping or range errors.

Epidata also has some limitations: a. Questionnaire files cannot exceed 999 lines of text; b. Epidata was not designed to be operated by multiple users. Only one person can modify a file at one time. But as the database I used did not exceed 100 lines of text and there was no need for more than two operators working at the same time, the limitations did not affect data entry.

Another method to minimise the error rate was double data entry. Double data entry can enhance the data quality, but it also substantially increases the cost and time of data entry. For these reasons, only 10% of the overall data was selected for double entry in Epidata. Compared with 198,400 data fields in total in my questionnaire, double data entry was only completed for 10% of them (19,840 data fields), having the potential to have less error (0.22% vs. 0.14% per data field respectively) due to a decreased amount of data entry work. But still, the single data entry error rate was not high compared with international health studies (see below). The limitation was that I could not ensure the other the 90% of the single entry data was completely accurate, which might undermine the validity of the data.

Data entry in previous studies

A few studies have reported the error rate of single data entry, which ranged from 0.04% to 0.34% per field. As no golden rule for the acceptable error rate exists, one way to assess my survey would be through comparison with similar studies discussed below (systematic review or meta-analysis have not been found in this area). Errors were determined by many factors: data field type (numeric or categorical), data field amount, data entry program, etc.

- The Coronary Artery Risk Development in Young Adults study in 1992 [240]
    - The single data entry error rate was 0.22% per field.
    - The sample size was 717 with 474,164 fields in the database (the dietary form, questions including serving size and amount, frequency in day, week or month, etc.).
    - A precoded screen was developed for data entry. No further information on the data entry program was reported.
- The Continuous Hyperfractionated Accelerated Radiotherapy Trials in 1994 [241]
    - The error rate of single data entry was 0.15% per field.
    - The sample was 44 patients with around 16,277 fields in the database.
    - The data entry manager was not mentioned.
- A recent clinical study in 2012
    - The error rate for single data entry was 0.04% based on Optical Mark Recognition automated forms processing [242].
    - The sample size was 398, and 21,608 data fields were in the database.
    - Epidata was used for data entry.
- A 2003 study [243]
    - The single data entry error rate was 0.34% per field.
    - The sample size was 560 and there were 104,720 fields in the database.
    - Data was entered by Microsoft Access.

The database in my survey had 198,400 data fields, and the single data entry error rate was 0.22%, which comparable with previous reported studies.

Data analysis

The use of factor analysis in the attitude section may lead to information being lost by grouping some sets of variables together. There was also a degree of subjectivity in deciding how many factors to include, which should be excluded, and how to categorise variables into different groups. But as the Health Belief Model was applied to generate attitude questions based on the five concepts, questions dealing with the same concept would have similar characteristics and responses. Thus, this would facilitate the extraction of factors and increase the exactness and practicality of the factors.

Data analysis methods used in other similar studies

Factor analysis is widely used in dietary pattern studies based on cultural background and diet preference [244]. It was also used in identifying stigma related to sexually transmitted diseases [218]. Despite the extraction of factors, researchers translated factor scores into quartiles, and then comparisons were made by logistic regression between the newly identified factors (dietary patterns and different levels of stigma, recoded as quartiles) and relevant variables, such as disease or health-seeking behaviours.

My survey is the first study I am aware of that uses factor analysis to find predictors of acceptability of HPV vaccines based on the Health Belief Model. I aimed to explore specific attitudes towards HPV vaccines (i.e. concerns about cost, side-effects, and risk), but I also wanted to find predictors of the acceptance of HPV vaccines from different emotional or psychological perspectives (such as perceived barriers and perceived effectiveness).

4.7.4 Comparisons with other studies

I compare my findings with studies carried out in Asian and Western countries below. To provide context, the issues below may affect the reliability of comparisons.

1) The status of the HPV vaccine (i.e. introduced or not, free or not)

- Studies prior to and after HPV vaccination may present different knowledge and attitudes [245, 246]
- The health insurance coverage would influence the acceptability of the vaccine [245, 247]

2) Disparity in demographics (gender, ethnicity, cultural background, etc.)

In the Asia-Pacific area, three countries (Australia [84], Singapore [84] and Malaysia [245]) introduced the HPV vaccine free of charge for recipients in 2006–2010. It is included in their National Immunization Programmes and the uptake is high (over three-quarters) [84]. A few countries and regions (e.g. Japan [247], South Korea [246], Hong Kong [248]) marketed the vaccine in 2006–2010, but the potential recipients had to order or request it in private health centres and meet the cost ($240–$500) on their own. The uptake of the vaccination is estimated at less than 10% in these Asia-Pacific regions, but unavailable and incomplete population data may also contribute to the low uptake [85].

Findings consistent with my survey

Findings consistent with those of my survey were found in previous studies carried out in China and other Asian and Western regions. These included: a low level of awareness of HPV, a high level of acceptability of HPV vaccines, and attitudes towards stigma and the influence of other people.

Low level of HPV awareness

Chinese adult women: Li's study carried out among 14–59-year-old Chinese women between 2005 and 2007 reported a low level of awareness (15.5%) [124]. It can be viewed as a robust study —a multi-centre, population-based questionnaire survey including rural regions which employed non-randomised cluster sampling and quota sampling methods. However, survey respondents were mostly adult women, and the low level of awareness might be attributed to the following features of the study: the early study period and the proportion of rural population (50%).

Chinese young adults: Two multi-centre Chinese studies [128] (surveyed in 2011–2012) explored the awareness of HPV in young adults (college students aged 18–22 years), and one study included approximately 50% males [129]. Low levels of awareness were found (14.3% in males, 7.2% in females). Both studies were conducted in urban regions of developed cities in China (some were the capital of a province).

Hong Kong Chinese teenagers: No other literature has been found that reported on knowledge and attitudes towards HPV infection among mainland Chinese teenagers. There are comparable studies among teenagers in Hong Kong. An HPV awareness level of 0% was found in 13–20-year-old girls in a focus group study in 2008 after HPV vaccines had been marketed in 2006 in Hong Kong [209]. This extremely low level of awareness may be explained by the early date of the research and the features of focus group. It might also be attributed to a similar culture to that of mainland China, in which females are supposed to be conservative regarding sexual issues and may be too shy to state in front of a group that they know about HPV infection.

Other Asian teenagers and young adults: Awareness regarding HPV was reported to be 21.7% among female university students (mean age 21.5 years) in Malaysia in 2010 [249] after HPV vaccinations were introduced.

High level of acceptability of the vaccine

Chinese adult women: Zhao's study, carried out in China in 2012, reported that the acceptability of HPV vaccination was 77% for women aged 15–59 years [201]. Li's study in 2009 found it to be 84.6% among 14–59-year-old Chinese women [124]. Kwan's study in 2008 found that the acceptability of HPV vaccination was 88% among Chinese women in Hong Kong [208].

Other Asian teenagers and young adults: Oh's study, carried out in South Korea [198] in 2010, (HPV vaccination was marketed in Korea in 2010) found the acceptability was 55.5% among adult women, and higher, 77%, for their daughters.

Predictors for the acceptability of HPV vaccine

Li' s study in China in 2009 reported [124] that for adult women, recommendations from doctors or nurses and hospital lecturers (46.2% to 55.6%.) were the major influences on accepting the HPV vaccine. This suggests that parents of teenagers in China would be open to recommendations of health professionals. The findings of my survey suggested that the recommendations Chinese teenagers would be most likely to take were those of their parents or doctors.

Brewer's systematic review, carried out in 2007 in the United States, also identified predictors for the acceptability of the HPV vaccine [121]. Higher perceived effectiveness (benefits), school requirements, and physician recommendation were associated with higher HPV vaccine acceptability. Higher perceived barriers were associated with lower HPV vaccine acceptability [121]. These were all similar to my findings, although a higher perceived severity of HPV infections was not related to greater vaccine acceptability[121].

Attitudes on stigma about HPV infection

Kwan's study carried out in Hong Kong in 2012 examined stigma about HPV infection among health professionals, including doctors, nurses, and smear-taking trainees, and thus might not comparable to the respondents of my survey [187]. The most commonly identified stigma was 'women are infected because they have more than 1 sexual partner' (32%).

Similarly, 29.5% of participants in my survey believed that people infected with HPV were promiscuous, and 17% of participants agreed that the partners of those infected with HPV infected had been unfaithful.

Stigma about HPV infection was negatively associated with the level of knowledge of HPV in both my study, and the Hong Kong study [187]. However, no evidence was found that stigma could be reduced by imparting knowledge to the recipients. Further studies are needed to find out what kind of knowledge is most effective in decreasing stigma associated with HPV.

Findings that differed from my results

However, there are some difference between findings in the Chinese and English literature and the findings of my survey. These included a higher level of awareness and knowledge of HPV and vaccination, a lower level of acceptability of the HPV vaccine, and different attitudes towards the HPV vaccination.

Moderate to high level of HPV awareness

Chinese adult women: In some recent multi-centre studies a moderate to high level of HPV awareness has been found (25.1% in a study on parents in 2013; 36% in a study on urban women in 2012) [123, 201]. A reason for this might be that the participants in both studies were from urban regions or even the capital of a province, where people are more likely to have a high level of education, income, and access to health care [123, 201].

Hong Kong Chinese teenagers: A moderate level of awareness of HPV (44%) was found in teenage girls in 2011. The research period (my survey was carried out in 2014, 3 years later) and method (self-administered questionnaire) might partly explain the difference between the awareness level among Hong Kong teenagers and that found in my survey [250]. The different levels of sexual health education and HPV vaccination campaign may also contribute to the difference in the awareness of HPV. Further studies are suggested to explore the issue.

Taiwanese young adults: An awareness level of HPV of 49% was found in 17–36-year-old Taiwanese young adults in 2011 [251].

Moderate level of acceptability of the vaccine

Young adults in West Asian countries: Ortashi's study carried out in 2012 in United Arab Emirates showed the acceptability of the vaccine was 46% among male university students (mean age: 21±1.5 years) [252].

Young adults in Western countries: It was 48% for young adults in the Netherlands in 2008 (age range 18–25 years; 91% were born in the Netherlands) [253]. A lower acceptability was found in the US—34% among young adults in 2008 (age range 18–32 years; 85.5% were white)[254].

Chinese parents of adolescents: 36.2% of the parents wanted to vaccinate their child in a 2013 multi-centre Chinese study [123]. Nearly 50% of the parents were wealthy, and 42.4% of them had higher than senior high school education. An explanation for the moderate acceptability provided in the study was that caution and hesitation regarding vaccination acceptance may be more emphasised among highly educated parents, as they may be exposed to a wider variety of environment and be influenced by more factors (eg pros and cons). However, further studies in China are needed on this issue concerning the education level and acceptability of HPV vaccination.

High level of knowledge

Young adults in Western countries: The knowledge that HPV is sexually transmitted is common among some Western young adults: 86–92% of 17–25-year-old students in the UK [255] in 2009, and 64.9% of 18–26-year-old Italian women [206] in 2012. 74.1% of them knew that HPV may cause cervical cancer [206]. The HPV vaccine was introduced to Italy in 2007 for girls aged 11. However, 4-8% of Chinese teenagers (30-60% of HPV-awarded respondents knew) in my survey had this knowledge.

Difference in gender in awareness and knowledge

A university-based study in 18–25-year-old Dutch young adults showed that females (17.7%) were more aware of HPV than males (12.1%) [253] and females (41.6%) answered more questions correctly than males (21.7%) in terms of HPV-related knowledge[248]. My survey had inconsistent results: no significant gender difference was identified in the awareness of HPV (14.6% vs. 12.4%).

Perceived risk of HPV and cervical cancer

The perceived risk of HPV among adult Korean men and women is 17.3% and 21.6% respectively [198], higher than that in my survey (8.6%).

Perceived benefits of the HPV vaccine

Compared to the 63.7% of participants who agreed that HPV vaccines would help avoid cervical cancer in my survey, 82.5% of Philippines [199] women (18–52 years old) believed the HPV vaccine could offer protection against cervical cancer in 2010. But in Sweden [200], only 6.3% of women aged 18–30 years old perceived the benefits after four years of the vaccine being approved for use. The reason for this low level of perceived benefit was not clear.

Perceived barriers to the HPV vaccine

Asian adult women: [198] 0.8–5.2% of Korean women were concerned by the adverse events of vaccination. 37.0% and 27.5% of Philippines women [199] worried about fatigue and long-term illness. Compared with the worry (71.5% worried about minor side effects) identified in my survey, Chinese people demonstrated more doubts about the side effects of the vaccine than other Asians.

Willingness to pay US$300 for the vaccine

Only 4% of adult males and females aged over 20 in Korea were willing to pay more than US$300 [198] and 28% Canadians aged 26-30 year old would want to pay US$300 for the three-dose vaccines. Zhang's study [123] in 2013 found 11.6% of Chinese parents of young adolescents were willing to pay more than CNY¥500.

Trust in drug companies

Very few Chinese teenagers (34.2%) in my survey trusted pharmaceutical companies. In Philippines [199], 87.4% of women trusted the companies that manufacture the vaccines. But comparison was difficult to make as neither of the studies mentioned whether the companies were national or international (i.e. Western pharmaceutical companies).

4.8 Conclusion

This questionnaire survey is among the first carried out among Chinese teenagers regarding their attitudes towards HPV vaccines based on the Health Belief Model; it was also among the first to identify positive/negative factors affecting the acceptability of HPV vaccines, and to explore HPV-related stigma among Chinese teenagers. Similarities as well as differences are found compared to results of similar work in the international literature. In contrast with teenagers in many other countries, I found that the Chinese teenagers in my survey had a low level of awareness and knowledge of HPV and cervical cancer, and conservative attitudes towards sexually transmitted infections. This may reflect the impact of traditional Chinese culture, social recognition, and acceptability on teenagers.

Based on the methodological limitations of the survey in terms of sampling and questionnaire design, further studies should explore more to fill in the gaps.

- Although this study in Heilongjiang province does provide evidence that will be likely be broadly representative of similar provinces located in central regions of China, multi-centre population-based studies among teenagers across China would be more representative.
- Participants in the survey were limited to public high school students. Vocational and private school students, who account for a significant proportion of the total number of students, also need to be studied.
- Social-economic questions and questions about family background were not included in the questionnaire because of pragmatic considerations and the response burden, but if applicable, further studies would need to identify the influences of social-economic status on the acceptance of HPV vaccines.

Box. Summary of findings in the questionnaire survey in China

Knowledge and attitude

Overall, this survey identified a low level of awareness of HPV infection and a high level of acceptability of HPV vaccine in the survey population.

The attitudes towards HPV infection and vaccination (including Health Belief Model constructs and stigma)

- The biggest worry (concerning both HPV infection, and cervical cancer) is health impact (72-80%)
- The greatest concern is minor side effects (72%)
- The most significant recommendation would be taken from their parents (66%)
- The biggest stigma is concern about gossip from others (51%)

Predictors for the acceptability of HPV vaccine

- Facilitators: Others' influences, perceived severity of HPV infection and cervical cancer, perceived benefits of HPV vaccine, high knowledge level of HPV infection and cervical cancer

Predictors for knowledge of HPV infection and vaccination

- Positive: perceived severity of HPV infection and cervical cancer
- Negative: stigma on HPV-infected people

Predictors for the awareness of HPV infection

- Positive: other influences on accepting HPV vaccines

Differences by responder characteristics

Gender

- Females had a higher level of acceptability of HPV vaccine
- Females were more concerned about the health impact, side effects, and parents' opinions
- Males were more concerned about the HPV vaccine leading to more sexual partners, cost of vaccination
- Males had more trust in drug companies
- Males had more knowledge about condoms protecting against HPV infection

Rurality

- Rural residents had lower level of awareness

Gaps

The gap with other Asian and Western countries

Countries and regions that have included the vaccination into national programmes

Countries and regions that have introduced the vaccination, but paid for by the recipients

Table 4-1: Selection and distribution of participants among five high schools

School	Number of classes	Number of classes in each grade (10,11,12)	Number questionnaires distributed	Number of respondents
No. 1 high school	13	5,4,4	776	723
No. 2 high school	14	5,5,4	844	767
No. 3 high school	13	5,4,4	782	757
Ning'an high school	13	4,5,4	792	742
Hailin high school	14	5,5,4	846	799
Total	67	24,23,20	4050	3788

Table 4-2: Characteristics of participants

Characteristic		Number	Percentage %
No. of participants	No. of approached	4050	
	No. of respondents	3788	92.2%
Age	14	2	0.1
	15	67	1.8
	16	519	13.7
	17	1261	33.3
	18	1195	31.5
	19	485	12.8
	20	175	4.6
	21	7	0.2
	22	2	0.1
	Missing	75	2.0
Gender	Male	1676	44.2
	female	2060	54.4
	Missing	52	1.4
Residence	Urban	3048	80.5
	Rural	740	19.5
	Missing	0	0
High school	No.1 high school	722	19.1
	No.2 high school	767	20.2
	No.3 high school	757	20.0
	Hailin high school	799	21.1
	Ning'an high school	743	19.6
	Missing	0	0
Smoking	Never	3200	84.5
	Once or twice	223	5.9
	Used to smoke, given up	89	2.3
	Sometimes	131	3.5
	Everyday	84	2.2
	Missing	61	1.6

Table 4-3: Characteristics of participants among urban/rural and male/female and <18/>=18 years old students

Characteristic	Urban	Rural	P value	Male	Female	P value	<18	>=18	P value
	N (%)	N (%)		N (%)	N (%)		N (%)	N (%)	
No. of participants	3048 (80.5)	740 (19.5)		1676 (44.2)	2060 (54.4)				
Age group			<0.001*			0.575			-
< 18	1591 (52.7)	258 (37.3)		837 (50.3)	1012 (49.4)		-	-	-
>= 18	1430 (47.3)	434 (62.7)		826 (49.7)	1038 (50.6)		-	-	-
Gender			0.671			-			-
Male	1363 (45.0)	313 (44.1)		-	-	-	-	-	-
female	1664 (55.0)	396 (55.9)		-	-	-	-	-	-
Residence			-			0.671			-
Urban	-	-	-	1363 (81.3)	1664 (80.8)		-	-	-
Rural	-	-	-	313 (18.7)	396 (19.2)		-	-	-
High school						0.007*			<0.001*
No. 1	722 (23.7)	0		351 (20.9)	371 (18.0)		427 (23.1)	295 (15.8)	
No. 2	767 (25.2)	0		343 (20.5)	424 (20.6)		427 (23.1)	340 (18.2)	
No. 3	757 (24.8)	0		340 (20.3)	410 (19.9)		383 (20.7)	367 (19.7)	
Hailin	379 (12.4)	420 (56.8)		357 (21.3)	414 (20.1)		166 (9.0)	587 (31.5)	
Ning'an	423 (13.9)	320 (43.2)		285 (17.0)	441 (21.4)		446 (24.1)	275 (14.8)	
Smoking			0.187			<0.001*			<0.001*
Never	2610 (81.6)	590 (18.4)		1294 (77.5)	1905 (92.6)		1639 (88.6)	1549 (83.1)	
Once or twice	177 (79.4)	46 (20.6)		139 (8.3)	84 (4.1)		94 (5.1)	129 (6.9)	
Used to, given up	73 (82.0)	16 (18.0)		63 (3.8)	26 (1.3)		36 (1.9)	53 (2.8)	
Sometimes	96 (73.3)	35 (26.7)		100 (6.0)	31 (1.5)		52 (2.8)	77 (4.1)	
Everyday	68 (81.0)	16 (19.0)		73 (4.4)	11 (0.5)		28 (1.5)	55 (3.0)	

By Chi-square testing, * $P<0.025$.

*Current: current smoker

Table 4-4: Difference of gender and age in smoking habits

Smoking	Male (ref.) N (%)	Female N (%)	P value	AOR (95% CI)	<18 (ref.) N (%)	>=18 N (%)	P value	AOR (95% CI)
Never (ref.)	1294 (77.5)	1905 (92.6)		1.00	1639 (88.6)	1549 (83.1)		1.00
Once or twice	139 (8.3)	84 (4.1)	<0.001*	0.40 (0.31-0.54)	94 (5.1)	129 (6.9)	0.007*	1.47 (1.11-1.94)
Used to, given up	63 (3.8)	26 (1.3)	<0.001*	0.28 (0.18-0.44)	36 (1.9)	53 (2.8)	0.029	1.62 (1.05-2.50)
Sometimes	100 (6.0)	31 (1.5)	<0.001*	0.20 (0.13-0.30)	52 (2.8)	77 (4.1)	0.018*	1.56 (1.08-2.24)
Everyday	73 (4.4)	11 (0.5)	<0.001*	0.10 (0.05-0.19)	28 (1.5)	55 (3.0)	0.001*	2.19 (1.37-3.49)

*P<0.025.

[b]AOR: adjusted odds ratio; 95%CI: 95% confidence interval.

Adjusted for age, gender, rurality, and schools

Table 4-5: Knowledge level of HPV and vaccination among respondents who had heard of HPV

Knowledge		Correct N (%)	Incorrect N (%)	Don't know N (%)	Missing N (%)
HPV	May cause cervical cancer (T)	327 (65.5)	52 (10.4)	113 (22.6)	7 (1.4)
	Can be cleared without treatment (T)	116 (23.2)	267 (53.5)	109 (21.8)	7 (1.4)
	Can last years without treatment (T)	342 (68.5)	46 (9.2)	102 (20.4)	9 (1.8)
	Can be sexually transmitted (T)	290 (58.1)	74 (14.8)	125 (25.1)	10 (2.0)
	Is an uncommon sexually transmitted infection in China (F)	212 (42.5)	129 (25.9)	148 (29.7)	10 (2.0)
The risk of HPV	Can be lowered by condom use (T)	199 (39.9)	134 (26.9)	156 (31.3)	10 (2.0)
	Can be increased by poor personal hygiene (F)	30 (6.0)	406 (81.4)	54 (10.8)	9 (1.8)
	Can be increased by having multiple sexual partners (T)	343 (68.7)	35 (7.0)	114 (22.8)	7 (1.4)
	Can be increased by early age at first sexual intercourse (T)	280 (56.1)	55 (11.0)	156 (31.3)	8 (1.6)
Knowledge about screening and vaccination	Cervical screening can effectively prevent cervical cancer (T)	342 (68.5)	63 (12.6)	82 (16.4)	12 (2.4)
	Regular cervical screening is not necessary after HPV vaccination (F)	351 (70.3)	61 (12.2)	79 (15.8)	8 (1.6)
	HPV test can identify women who are at increased risk of cervical cancer (T)	296 (59.3)	54 (10.8)	141 (28.3)	8 (1.6)
	HPV vaccination is 100% effective against cervical cancer (F)	366 (73.3)	41 (8.2)	84 (16.8)	8 (1.6)
	HPV vaccination are most useful for those who already have had sex (F)	206 (41.3)	73 (15.6)	212 (42.5)	8 (1.6)

*F: the correct answer is false; T: the correct answer is true. 499 participants who had heard of HPV were supposed to answer the knowledge questions.

Table 4-6: Attitudes towards HPV infection and vaccination among all the participants

Attitudes		Very unlikely	Somewhat unlikely	Somewhat likely	Very likely	Unsure	Missing
How likely is the perceived risk of…	HPV infection in the future	1219 (32.2)	1198 (31.6)	298 (7.9)	27 (0.7)	1039 (27.4)	7 (0.2)
	Cervical cancer in the future	531 (25.8)	644 (31.3)	134 (6.5)	17 (0.8)	718 (34.9)	16 (0.8)
		Strongly disagree	Somewhat disagree	Somewhat agree	Strongly agree	Unsure	Missing
HPV would be disruptive to… (perceived severity)	Physical health	127 (3.4)	444 (11.7)	2197 (58.0)	524 (13.8)	492 (13.0)	4 (0.1)
	Social life	228 (6.0)	860 (22.7)	1650 (43.6)	441 (11.6)	605 (16.0)	4 (0.1)
	Sexual relationships	175 (4.6)	425 (11.2)	1760 (46.5)	614 (16.2)	806 (21.3)	8 (0.2)
Cervical cancer would be disruptive to (perceived severity)	Physical health (Female)	45 (2.2)	117 (5.7)	1178 (57.2)	469 (22.8)	240 (11.7)	11 (0.5)
	Social life (Female)	86 (4.2)	436 (21.2)	883 (42.9)	299 (14.5)	346 (16.8)	10 (0.5)
	Sexual relationships (Female)	70 (3.4)	223 (10.8)	955 (46.4)	330 (16.0)	472 (22.9)	10 (0.5)
If vaccinated, HPV vaccines… (perceived benefits)	Will help avoid HPV infection	66 (1.7)	161 (4.3)	2541 (67.1)	427 (11.3)	585 (15.4)	8 (0.2)
	Will help avoid cervical cancer	82 (2.2)	479 (12.6)	2091 (55.2)	323 (8.5)	776 (20.5)	37 (1.0)
	No longer necessary to be screened for cervical cancer (F)	435 (21.1)	1249 (60.6)	112 (5.4)	21 (1.0)	238 (11.6)	5 (0.2)
	May need less frequent screening for cervical cancer (F)	245 (11.9)	972 (47.2)	518 (25.1)	30 (1.5)	279 (13.5)	16 (0.8)
	May lead to having more sexual partners as the risk of disease is reduced	1289 (34.0)	1362 (36.0)	440 (11.6)	102 (2.7)	561 (14.8)	34 (0.9)
I am concerned that HPV vaccines … (perceived barriers)	Not have been proved effective to prevent cervical cancer	104 (2.7)	604 (15.9)	1806 (47.7)	195 (5.1)	1049 (27.7)	30 (0.8)
	May have minor side effects such as fatigue or fever	72 (1.9)	273 (7.2)	2363 (62.4)	344 (9.1)	724 (19.1)	12 (0.3)
	May have major side effects such as long term illness	160 (4.2)	910 (24.0)	1408 (37.2)	281 (7.4)	1010 (26.7)	19 (0.5)
	Cost too much and don't want to pay such a high cost	326 (8.6)	955 (25.2)	1258 (33.2)	440 (11.6)	800 (21.1)	9 (0.2)
	Trust the companies that make HPV vaccines	228 (6.0)	776 (20.5)	1175 (31.0)	120 (3.2)	1479 (39.0)	10 (0.3)
I would be vaccinated if these people recommend me to (Other influences)	Friends	169 (4.5)	815 (21.5)	1321 (34.9)	152 (4.0)	1322 (34.9)	9 (0.2)
	Parents	112 (3.0)	392 (10.3)	2088 (55.1)	415 (11.0)	774 (20.4)	7 (0.2)
	Doctors or nurses	149 (3.9)	442 (11.7)	1895 (50.0)	407 (10.7)	887 (23.4)	8 (0.2)
	School requirement	238 (6.3)	663 (17.5)	1519 (40.1)	227 (6.0)	1130 (29.8)	11 (0.3)
	Public service ads on TV or internet	478 (12.6)	977 (25.8)	897 (23.7)	120 (3.2)	1313 (34.7)	3 (0.1)
Attitudes on stigma	People will think that someone who is infected with HPV is a person who is promiscuous	320 (8.4)	1402 (37.0)	939 (24.8)	179 (4.7)	895 (23.6)	53 (1.4)
	If someone has HPV infection, people will gossip	269 (7.1)	844 (22.3)	1685 (44.5)	226 (6.0)	712 (18.8)	52 (1.4)
	People are infected as they/their partners have been unfaithful	411 (10.9)	1611 (42.5)	487 (12.9)	156 (4.1)	1070 (28.2)	53 (1.4)
	One should keep a social distance from those who are infected with HPV	280 (7.4)	1263 (33.3)	1170 (30.9)	193 (5.1)	830 (21.9)	52 (1.4)

F means these questions were only required to be answered by female students.

Table 4-7: Knowledge of HPV and vaccination: Gender, rurality, and age impact

Knowledge	Male (ref.) N (%)	Female N (%)	P value By χ^2	AOR[b] (95% CI) By logistic regression
Condom use lowers the risk of HPV infection				
Don't know	59 (24.5)	97 (39.1)		1.00
Incorrect	64 (26.6)	70 (28.2)		
Correct	118 (49.0)	81 (32.7)	<0.001*	0.56 (0.38-0.82)**
Poor personal hygiene can increase the risk of getting HPV infection				
Don't know	35 (14.5)	19 (7.6)		1.00
Incorrect	191 (79.3)	215 (86.3)		
Correct	15 (6.2)	15 (6.0)	0.049*	0.95 (0.44-2.04)
Early age at first sexual intercourse can increase the risk of getting HPV infection				
Don't know	75 (31.0)	81 (32.5)		1.00
Incorrect	38 (15.7)	17 (6.8)		
Correct	129 (53.3)	151 (60.6)	0.007*	1.31 (0.90-1.91)
HPV vaccination are most useful for those who already have had sex (F)				
Don't know	89 (36.8)	123 (49.4)		1.00
Incorrect	46 (19.0)	27 (10.8)		
Correct	107 (44.2)	99 (39.8)	0.005*	0.61 (0.36-1.06)
	Urban (ref.) N (%)	**Rural N (%)**	**P value By χ^2**	**AOR[b] (95% CI) By logistic regression**
Condom use lowers the risk of HPV infection				
Don't know	148 (32.5)	8 (24.2)		1.00
Incorrect	129 (28.3)	5 (15.2)		
Correct	179 (39.3)	20 (60.6)	0.049*	3.15 (1.41-7.04)**
	<18 (ref.) N (%)	**>=18 N (%)**	**P value By χ^2**	**AOR[b] (95% CI) By logistic regression**
Poor personal hygiene can increase the risk of getting HPV infection				
Don't know	35 (14.8)	19 (7.5)		1.00
Incorrect	189 (79.7)	216 (85.7)		
Correct	13 (5.5)	17 (6.7)	0.037*	1.27 (0.60-2.68)

*P<0.025 by chi-square, meaning there is difference in the distribution of responses;
F means the correct answer is false.

[b]AOR: adjusted odds of females/rural/>=18 participants who correctly answered the area of knowledge in contrast to those who did not (including both those who chose responses of 'Don't know' and 'Incorrect') by multivariate logistic regression; 95%CI: 95% confidence interval.

Adjusted for age, gender, rurality, and schools

Table 4-8: Attitudes of HPV and vaccination: gender impact

Attitudes	**Male (ref.) N (%)**	**Female N (%)**	**P value By χ^2**	**AOR[b] (95% CI) By logistic regression**
If I had an HPV infection, it would have a serious impact on my physical health				
Disagree	281 (16.8)	274 (13.3)		1.00
Unsure	229 (13.7)	256 (12.4)		
Agree	1165 (69.6)	1527 (74.2)	<0.01*	1.23 (1.06-1.43)**
Having an HPV vaccination may lead to people having more sexual partners as they think their risk of disease is reduced				
Disagree	1029 (62.3)	1581 (77.0)		1.00
Unsure	264 (16.0)	291 (14.2)		
Agree	358 (21.7)	180 (8.8)	<0.001*	0.36 (0.29-0.44) **
I am concerned that HPV vaccines have not been proved effective in prevention of HPV and cervical cancer				
Disagree	344 (20.8)	355 (17.3)		1.00
Unsure	438 (26.5)	595 (29.0)		
Agree	870 (52.7)	1105 (53.8)	0.016*	1.08 (0.95-1.24) **
I am concerned that HPV vaccines may have side effects such as fatigue or fever				
Disagree	181 (10.8)	160 (7.8)		1.00
Unsure	332 (19.9)	384 (18.7)		
Agree	1156 (69.3)	1511 (73.5)	0.002*	1.22 (1.06-1.42) **
I am worried that the HPV vaccine costs too much (¥2000) and I don't want to pay such a high cost for the vaccine				
Disagree	553 (33.1)	711 (34.6)		1.00
Unsure	300 (18.0)	489 (23.8)		
Agree	817 (48.9)	857 (41.7)	<0.001*	0.76 (0.67-0.87) **
I trust the companies that make HPV vaccines				
Disagree	462 (27.7)	533 (25.9)		1.00
Unsure	558 (33.4)	895 (43.5)		
Agree	649 (38.9)	629 (30.6)	<0.001*	0.70 (0.61-0.80) **
I would get vaccinated if my parents recommend me to do so				
Disagree	264 (15.8)	236 (11.5)		1.00
Unsure	334 (20.0)	429 (20.9)		
Agree	1075 (64.3)	1391 (67.7)	<0.001*	1.19 (1.03-1.37) **
I would get vaccinated if doctors or nurses recommend me to do so				
Disagree	316 (18.9)	271 (13.2)		1.00
Unsure	361 (21.6)	510 (24.8)		
Agree	997 (59.6)	1274 (62.0)	<0.001*	1.09 (0.96-1.25)
I would get vaccinated if there is a school requirement for me to be vaccinated				
Disagree	468 (28.0)	424 (20.7)		1.00
Unsure	451 (27.0)	658 (32.1)		
Agree	754 (45.1)	970 (47.3)	<0.001*	1.12 (0.98-1.29)

*P<0.025 by chi-square, meaning the there is difference in the distribution of responses;
**p<0.025 by logistic regression.
[b]AOR: adjusted odds of females who agreed the attitudinal statement in contrast to those who did not (including both those who chose responses of 'Disagree' and 'Unsure) by multivariate logistic regression; 95%CI: 95% confidence interval.
Adjusted for age, gender, rurality, and schools

Table 4-8: continued

Attitudes	**Male (ref.) N (%)**	**Female N (%)**	**P value By χ^2**	**AOR[b] (95% CI) By logistic regression**
People are infected because they or their partners have been unfaithful				
Disagree	909 (54.4)	1107 (53.8)		1.00
Unsure	437 (26.2)	631 (30.7)		
Agree	325 (19.4)	318 (15.5)	0.001*	0.81 (0.68-0.97)
If I had an HPV infection, it would be disruptive to my sexual relationship(s)				
Disagree	285 (17.1)	304 (14.8)		1.00
Unsure	310 (18.6)	481 (23.4)		
Agree	1075 (64.4)	1273 (61.9)	<0.001*	0.91 (0.79-1.04)
I would get vaccinated if my friends recommend me to do so				
Disagree	459 (27.4)	511 (24.9)		1.00
Unsure	501 (29.9)	804 (39.2)		
Agree	714 (42.7)	738 (35.9)	<0.001*	0.80 (0.70-0.92) **
I would get vaccinated if public service ads on TV or internet recommend it				
Disagree	664 (39.6)	771 (37.5)		1.00
Unsure	523 (31.2)	770 (37.4)		
Agree	488 (29.1)	517 (25.1)	<0.001*	0.84 (0.72-0.97) **
How likely is the risk that you will be getting HPV in the future				
Unlikely (ref.)	1107 (66.2)	1281 (62.2)		1.00
Unsure	399 (23.9)	619 (30.1)		
Likely	165 (9.9)	158 (7.7)	<0.001*	0.83 (0.65-1.05)

*P<0.025 by chi-square, meaning the there is difference in the distribution of responses; **p<0.025 by logistic regression.

[b]AOR: adjusted odds of females who agreed the attitudinal statement in contrast to those who did not (including both those who chose responses of 'Disagree' and 'Unsure) by multivariate logistic regression; 95%CI: 95% confidence interval.

Adjusted for age, gender, rurality, and schools

Table 4-9: Results of logistic regression: differences by age, gender, rurality and smoking in the acceptability of the HPV vaccine, awareness of HPV and knowledge level of HPV infection and vaccination.

		Likely to be vaccinated			Had heard of HPV(the screening question)			Had high level of knowledge		
		N (%)[a]	AOR[b] (95% CI)	P- value	N (%)[a]	AOR[b] (95% CI)	P- value	N (%)[a]	AOR[b] (95% CI)	P- value
Age	<18 (ref.)	1222 (66.1)	1.00		241 (13.0)	1.00		104 (45.2)		
	>=18	1302 (70.0)	1.21(0.99-1.47)	0.068	257 (13.8)	1.16(0.95-1.40)	0.143	117 (47.6)	1.15(0.80-1.67)	0.477
Gender	Male (ref.)	1110 (66.3)	1.00		244 (14.6)	1.00		111 (47.2)		
	Female	1431 (69.5)	1.69(1.38-2.07)	<0.001*	255 (12.4)	0.92(0.76-1.12)	0.411	111 (45.9)	0.87(0.60-1.27)	0.476
Rurality	Urban (ref.)	2068 (67.9)	1.00		466 (15.3)	1.00		206 (46.2)		
	Rural	507 (68.9)	0.77(0.56-1.04)	0.090	33 (4.5)	0.33(0.22-0.49)	<0.001*	16 (51.6)	1.80(0.81-3.98)	0.148
Smoking	Never (ref.)	2150 (67.3)	1.00		404 (12.6)	1.00		187 (48.6)	1.00	
	Once or twice	170 (76.6)	1.32 (0.86-2.03)	0.206	30 (13.5)	1.09 (0.73-1.63)	0.686	9 (32.1)	0.56 (0.24-1.29)	0.173
	Used to, given up	63 (70.8)	0.88 (0.49-1.58)	0.676	21 (23.6)	2.09 (1.25-3.49)	0.005*	8 (38.1)	0.63 (0.25-1.56)	0.315
	Sometimes	91 (69.5)	1.04 (0.62-1.76)	0.876	23 (17.6)	1.62 (1.01-2.61)	0.048	10 (43.5)	0.81 (0.34-1.95)	0.640
	Everyday	59 (70.2)	0.97 (0.52-1.80)	0.921	20 (23.8)	2.17 (1.27-3.68)	0.004*	7 (36.8)	0.62 (0.23-1.64)	0.330
Had heard of HPV	No (ref.)	2221 (67.6)	1.00		-	-	-	-	-	-
	Yes	354 (71.2)	0.85(0.72-1.25)	0.698	-	-	-	-	-	-
Knowledge level	Low (ref.)	160 (63.2)	1.00		-	-	-	-	-	-
	High	179 (80.6)	2.43(1.39-4.25)	0.002*	-	-	-	-	-	-

[a]N means the number of respondents likely to be vaccinated/had heard of HPV/had high level of knowledge and (%) means the proportion in each category (e.g. the proportion of respondents who had heard of HPV in all the never-smoke respondents).

Multivariate logistic regressions were performed. *P<0.025

[b]AOR: adjusted odds ratio; 95%CI: 95% confidence interval

Adjusted for age, gender, rurality and schools, and awareness, smoking

Table 4-10: Results of factor analysis on attitudes towards HPV vaccine

Variables	Factor				
	1	2	3	4	5
1. I would get vaccinated if my friends recommend me to do so	0.782	-	-	-	-
2. I would get vaccinated if my parents recommend to do so	0.715	-	-	-	-
3. I would get vaccinated if doctors or nurses recommend me to do so	0.740	-	-	-	-
4. I would get vaccinated if there is a school requirement for me to be vaccinated	0.775	-	-	-	-
5. I would get vaccinated if public service ads on TV or internet recommend it	0.706	-	-	-	-
6. People will think that someone who is infected with HPV is a person who is promiscuous	-	0.769	-	-	-
7. If someone has HPV infection, people will gossip	-	0.770	-	-	-
8. People are infected because they or their partners have been unfaithful	-	0.811	-	-	-
9. One should keep a social distance from those who are infected with HPV	-	0.524	-	-	-
10. I'm concerned that HPV vaccines have not been proved effective in prevention of HPV and cervical cancer	-	-	0.740	-	-
11. I'm concerned that HPV vaccines may have side effects such as fatigue or fever	-	-	0.651	-	-
12. I'm concerned that HPV vaccines may have major side effects such as long term illness	-	-	0.746	-	-
13. I'm worried that HPV vaccine costs too much	-	-	0.663	-	-
14. If I had an HPV infection, it would have a serious impact on my physical health	-	-	-	0.799	-
15. If I had an HPV infection, it would be disruptive to my social life	-	-	-	0.846	-
16. If I had an HPV infection, it would be disruptive to my sexual relationship	-	-	-	0.779	-
17. If someone is vaccinated with HPV vaccine, this will help them avoid HPV infection	-	-	-	-	0.847
18. If someone is vaccinated with HPV vaccine, this will help them avoid cervical cancer	-	-	-	-	0.843
Eigenvalues	5.94	2.05	1.46	1.43	1.14
Variance (%)	29.68	10.24	7.32	7.13	5.70
Cumulative Variance (%)	29.68	39.92	47.24	54.37	60.07

Extraction Method: Principal Component Analysis.
Rotation Method: Varimax with Kaiser Normalization.
Only factor loadings over 0.40 is shown in the table

Table 4-11: The attitudinal predictors for acceptability of HPV vaccines, HPV awareness and knowledge

Attitudes	Quartile	Likely to be vaccinated (N=)		Had heard of HPV (N=)		Had high level of knowledge[a] (N=)	
		AOR[b] (95% CI)	P- value	AOR[b] (95% CI)	P- value	AOR[b] (95% CI)	P- value
Other influences	1 (ref.)	1.00		1.00		1.00	
	2	0.85 (0.65-1.11)	0.230	1.27 (0.94-1.71)	0.118	1.21 (0.67-2.21)	0.527
	3	1.49 (1.12-1.98)	0.006*	1.65 (1.24-2.20)	0.001*	1.16 (0.66-2.06)	0.602
	4	3.89 (2.75-5.49)	<0.001*	1.66 (1.24-2.20)	0.001*	1.65 (0.94-2.89)	0.079
Perceived barriers	1 (ref.)	1.00		1.00		1.00	
	2	1.26 (0.93-1.71)	0.137	1.22 (0.92-1.63)	0.172	2.28 (1.28-4.04)	0.005*
	3	1.15 (0.85-1.56)	0.351	1.37 (1.04-1.82)	0.028	1.72 (0.98-3.01)	0.060
	4	0.75 (0.56-0.99)	0.045	1.34 (1.01-1.78)	0.041	1.34 (0.76-2.37)	0.317
Perceived severity	1 (ref.)	1.00		1.00		1.00	
	2	1.65 (1.26-2.16)	<0.001*	1.07 (0.82-1.39)	0.623	2.38 (1.40-4.04)	0.001*
	3	1.81 (1.38-2.38)	<0.001*	0.91 (0.69-1.20)	0.494	2.39 (1.39-4.12)	0.002*
	4	2.53 (1.87-3.42)	<0.001*	0.77 (0.58-1.02)	0.071	2.91 (1.66-5.13)	<0.001*
Perceived benefits	1 (ref.)	1.00		1.00		1.00	
	2	2.01 (1.53-2.64)	<0.001*	1.39 (1.05-1.84)	0.023*	1.31 (0.75-2.30)	0.346
	3	2.12 (1.61-2.79)	<0.001*	1.52 (1.15-2.01)	0.004*	1.53 (0.89-2.64)	0.126
	4	3.01 (2.22-4.08)	<0.001*	1.07 (0.80-1.44)	0.654	1.84 (1.02-3.32)	0.043
Stigma about HPV infection	1 (ref.)	-	-	1.00		1.00	
	2	-	-	1.28 (0.98-1.69)	0.075	1.20 (0.72-2.02)	0.486
	3	-	-	1.04 (0.78-1.38)	0.793	1.57 (0.91-2.71)	0.104
	4	-	-	1.06 (0.80-1.40)	0.711	0.48 (0.27-0.84)	0.011*

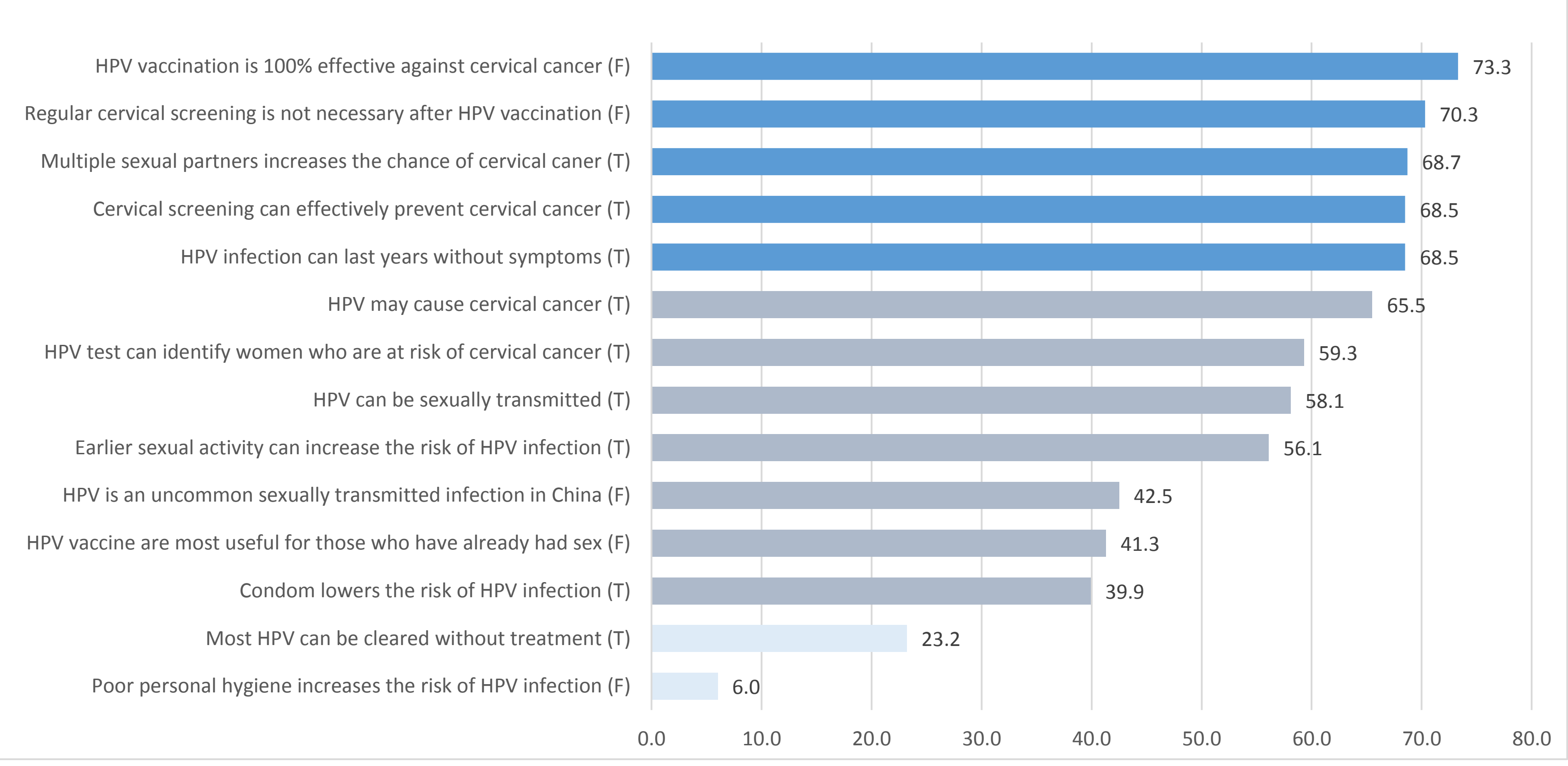
Multivariate logistic regressions were performed between acceptability of HPV vaccines and attitudes, awareness of HPV and attitudes, knowledge level and attitudes. *P<0.025.

[b]AOR: adjusted odds ratio; 95%CI: 95% confidence interval.

Adjusted for age, gender, rurality and schools, and awareness, smoking

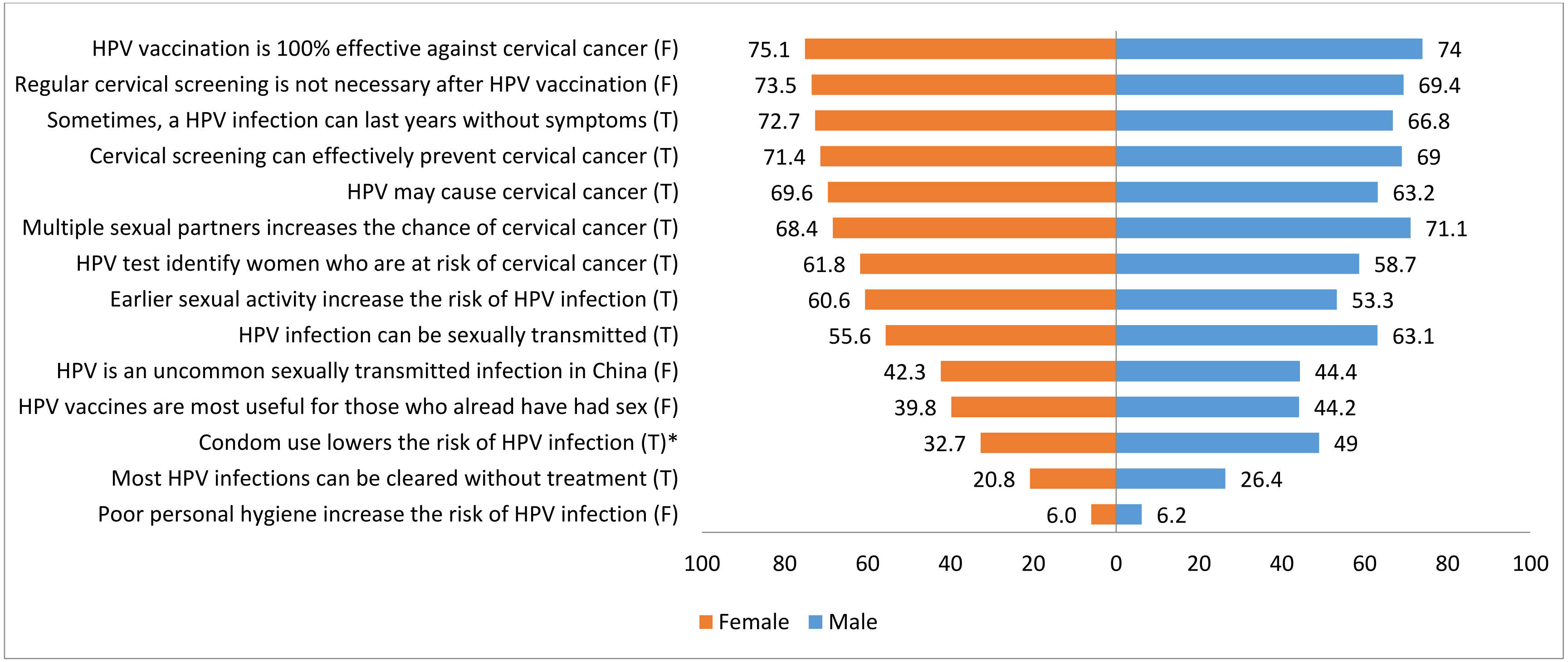
[a]: respondents had knowledge > 6 scores; 1: the lowest quartile; 4: the highest quartile;

Figure 4-1: Knowledge level of HPV and cervical cancer



F means the correct answer is false; T means the correct answer is true.
The percentage given close to the bar means the proportion of participants who correctly answered the knowledge question.

Figure 4-2: Knowledge level of HPV and vaccination between male and female students



* indicates significant difference of knowledge level between males and females
F means the correct answer is false; T means the correct answer is true.
The percentage given close to the bar means the proportion of participants who correctly answered the knowledge question

5 Chapter 5 Discussion and implications

5.1 Introduction

My thesis has examined an important element of any future strategy to reduce the burden from cervical cancer in China—the knowledge, attitudes, and beliefs of young people in relation to HPV vaccination and cervical cancer screening. I have emphasised in my thesis that cervical cancer is the fourth most common cancer in women worldwide, and the fourth most common in Chinese women. Further, there is an ongoing upward trend in the incidence of cervical cancer and HPV prevalence in China over the last decade [16].

Two major strategies for prevention of cervical cancer are available worldwide: cervical screening and HPV vaccination. HPV vaccination, which has been licenced and introduced in over 120 countries since 2006, is expected to prevent up to 70% of cervical cancer cases — it is widely viewed as a cost-effective prevention strategy. However, in China, no national cervical cancer prevention programmes have been established. Many factors contribute to this, including China's large geographic area and diverse population, and a lack of prioritisation of cervical screening. Hence, comprehensive but tailored prevention programmes need to be developed which include education, HPV vaccination, and cervical screening. Awareness and knowledge of HPV infection and vaccination—factors that would affect the acceptability of HPV vaccination in China—have not, to date, been thoroughly examined in China.

The primary aim of my thesis was to identify knowledge levels about HPV and vaccination and the attitudinal facilitators and barriers that would influence the introduction of HPV vaccination. Hence, I undertook a systematic review and a questionnaire survey, as described in Chapters 2, 3, and 4. In this chapter, I summarise my findings, examining methodological issues, and describe the main contributions of my thesis to the area of cervical cancer control in China. I include some recommendations for future research and examine some of the many factors which need to be taken into account if HPV vaccination is to be successfully introduced in China.

5.1.1 Summary of key outputs from my thesis

Chapter 2 described the methodology and results of the systematic review. Chapter 3 presented the methodology for my questionnaire survey, and Chapter 4 provided the results of my survey.

5.1.2 Summary of key outputs from my systematic review

My systematic review is the first exercise of its kind that I am aware of: it examines and synthesises research on knowledge of and attitudes towards HPV vaccination in the Chinese literature from various regions across China and among different population groups, including teenagers, adults, health professionals, and racial groups (such as Uyghur people).

Forty-seven studies were identified in my search. There were three key findings:
1) There are variations between different demographics and geographical areas in terms of awareness and knowledge of HPV infection, and the acceptability of HPV vaccination, suggesting the potential for health inequalities in more deprived regions (where there are less health care facilities and personnel).
2) There are many factors which would affect the acceptability of HPV vaccines.
3) There are significant issues in the quality of Chines studies when compared with international studies (this is discussed further in section 5.3 in this chapter).

A similar pattern in terms of demographics and location was identified in the awareness and knowledge of HPV infection and cervical cancer: for example, low levels of awareness of HPV (<10% of respondents in the included studies) were found among survey populations in West China, among underserved populations (Uyghur women and rural women), and among younger people (teenagers), while moderate levels of awareness of HPV (approximately 30% of respondents in the included studies) were found among young adults and urban adult women. In addition, differing patterns in acceptability of the vaccine were found: health professionals who had higher levels of awareness (>80%) and knowledge of HPV and cervical cancer (>80%) had a lower level of acceptability (<30%) of the HPV vaccine (for their daughters); people in North China who had a moderate level (about 30%) of awareness and knowledge of HPV and cervical cancer had a higher level acceptability (>70%) of the HPV vaccine for both themselves and their daughters.

It is important to note, however, that there are only a limited number of studies in each category and the fair or poor quality of these studies limits the confidence that can be placed in these results. Few studies (eight in total) examined factors affecting the acceptability of HPV vaccines: the cost of the vaccine, who would provide the vaccine, the source of the vaccine, and the acceptable age of vaccination were the most commonly examined factors. These studies suggest that the majority of respondents would be willing to pay up to ¥100 ($16) for the vaccine (>80% of respondents in the included studies), and would be willing to accept vaccines offered by the government (>55% of respondents in the included studies). Issues regarding the safety and effectiveness of HPV vaccines were examined in the included studies, but it is difficult to draw a definite conclusion because of the small number of studies (four) examining these topics, as well as the diverse populations and different wording of the questions included in these studies.

5.1.3 Summary of key outputs from my survey

My questionnaire survey differed from most previously published studies in China on this topic in that it developed a theory-based questionnaire to explore attitudes towards HPV vaccines among Chinese teenagers. It is also among the first to examine facilitators and barriers to the acceptability of HPV vaccines and HPV-related stigma among a school-age Chinese population.

There were three key findings:

1) low levels of awareness of HPV despite high levels of acceptability of HPV vaccination; varying levels of knowledge of HPV and cervical cancer (low, moderate, and high);

2) there are many predictors for the acceptability of HPV vaccines (e.g. perceived effectiveness of HPV vaccine; perceived barriers to HPV vaccine)

3) gender and age have a significant effect on awareness, knowledge, and attitudes

I found that the Chinese teenagers in my survey had a low level of awareness of HPV and high levels of acceptability of HPV vaccination. These results were consistent with findings in my systematic review. Attitudes towards sexually transmitted infections differed from those typically seen in Western literature, and may be explained by traditional Chinese culture and prevailing social norms.

I found both facilitators and barriers to acceptance of HPV vaccination among Chinese teenagers.

Four facilitators were found. These were:

- recommendations from parents and doctors
- perceived severity of HPV infection and of cervical cancer—the greater the physical, sexual or social impact respondents perceived, the more likely they were to accept HPV vaccination

- perceived benefits of HPV vaccine—the more effective respondents perceived HPV vaccination to be, the more likely they were to be vaccinated
- high levels of knowledge of HPV and cervical cancer.

Females reported higher levels of acceptability of HPV vaccines, and they were more concerned than males about the health impact of HPV infection and of cervical cancer, the side effects of vaccination, and the opinions of their parents. Males were more concerned about the cost of vaccination and the prospect of HPV vaccination leading to higher levels of sexual activity. Males also had more trust in drug companies and more knowledge of preventive measures such as condom use.

5.2 Methodological issues

In critiquing my findings I need to examine some key methodological issues, principally: 1) my search strategy and the critical appraisal and synthesis of results in my systematic review; and 2) the study design, instrument development, and analytical issues concerning data from my questionnaire survey. These issues inevitably affect the external and internal validity of my findings and reveal the strengths and weaknesses of the key outputs from my thesis.

5.2.1 Methodological issues in my systematic review

As with all systematic reviews, there are limitations which must be recognised. The search strategy had limitations with respect to the time period covered, languages included, and the locations of included studies. Searches of the databases (CNKI and Wanfang databases) selected for my systematic review were carried out in December in 2012; since that date there have been newly published Chinese-language publications (2013–2015) added to these two databases examining knowledge of and attitudes towards HPV and vaccination. Further, these more recent studies included more geographical regions, and broader areas of attitudes were explored. I will include this more recent evidence in the peer-reviewed paper based on this section.

Moreover, I did not include English literature and studies carried out in Hong Kong and Taiwan for the following reasons: English-language papers were mostly included in English-language systematic reviews, and studies carried out in Taiwan and Hong Kong were published either in English language or in Traditional Chinese language—a different written Chinese language from the Simplified Chinese language used in Mainland China databases like CNKI. Hence, the external validity of my review might be limited, but it provides valuable results that summarise the findings of surveys in Chinese-language literature carried out in Mainland China; international researchers may have only limited opportunity to access these findings.

Critical appraisal was carried out on included studies in order to assess their internal validity. I chose an existing quality assessment tool and modified it to better suit my review. There are obvious implications of using quality assessment tools developed in the context of western literature in reviews of papers in a different language and from a different culture. However, there is no gold standardised tool and I chose the quality assessment tool I believed to me the most appropriate for my review. As more and more scientific literature is produced in China, it is likely that quality assessment tools designed to reflect local literature will emerge. For the time being the only choice is to use western-developed tools, while trying to examine carefully whether their criteria seem appropriate for Chinese literature.

Based on the quality assessment, some of the included studies in my review were not of high quality, especially the surveys carried out in West China and among ethnic minority and teenage populations. A number of factors may contribute to this poorer quality of publications: 1) the different level of required quality for the journals in which these studies were published; 2) the lack of commonly applied standardised guidelines in performing and reporting studies, in contrast to much published research in Western literature; 3) the limited academic resources and network in the research institutes where these studies were carried out. Despite these issues, one strength of my review is that its quality assessment report is among the first to critically appraise Chinese-language studies carried out in Mainland China and thus may offer some insights for Chinese researchers to perform and publish higher-quality studies.

I used a narrative synthesis approach to describe my findings, displaying summaries of key findings in tables and graphs. For some items of interest only a few studies were available in which relevant data was reported (for example, people's concerns about the safety and effectiveness of HPV vaccines were reported in only four studies, carried out among different subgroups—health professionals, urban adults, and adult women, and using different wording in the questions (see Chapter 2)). Further discussion of the systematic review is provided later in this chapter (5.4)

5.2.2 Methodological issues in my survey

The external validity of my survey may be limited because of the selection of the location and participants. Although my survey was carried out in one province—Heilongjiang—the results could be generalised to some inland provinces in China, because of the similar demography, economy, and education level between them. Obviously, a larger sample size and random sampling might yield greater statistical power to achieve more accurate national estimates. I used a non-probability sampling method—convenience sampling—due to the availability of and easy access to the selected participants. It may be less representative than random or cluster sampling, but careful study design regarding the selection of classes, grades, and schools (inclusion/exclusion criteria applied) and the recruitment of participants may, to some extent, reduce the selection bias. Further, although I have made comparisons between knowledge and attitudes according to rurality, care should be taken in interpreting these results. There was a disproportionate participation rate of urban to rural participants in my survey, and because of this, my selected schools are not representative of the rest of the province with respect to rural/urban ratio.

My survey used a questionnaire designed specifically for this study to explore the issues of HPV vaccination in the school-age population. Hence, my study instrument had not been validated prior to my research. However, I consider I took reasonable measures to ensure the quality of my questionnaire; questions were generated based on western and Chinese literature review, and the wording of the questionnaire was refined by cognitive interviews in order to obtain more valid and reliable questions. I also invested considerable effort in designing questions, and forms of wording which were culturally and linguistically appropriate for my study setting.

I used a theory-based approach (the Health Belief Model) to formulate the questions in my questionnaire. As I've discussed the HBM might be limited in terms of the model's constructs and the model's application in my study setting. However, after reviewing available models, I considered the HBM to be the most appropriate for my study setting – its basic constructs seemed understandable to school-age children in China. A degree of caution is, nevertheless, necessary, as concepts such as fear, anxiety and vulnerability sometimes don't translate well between cultures.

One concern in questionnaires of this nature is multiple testing: there is no standardized correction to decrease the possibility of finding significant results by chance. In my analyses, I used the *Bonferroni* correction—the simplest and most conservative approach—to correct the observed p value significance level. Two main analyses of the hypothesis were performed: I sought to correct for multiple testing by dividing the p value by two hypothesis tests, and the new level of significance was 0.025. But for each analysis of the hypothesis, 14 tests were performed. If the *Bonferroni* correction was used for the 14 tests, then the new significant level of p value would be 0.004. Considering the significant level for sample size estimation and that a larger sample size would have been required if I had used this very small significant level (a sample approximately six times larger when using a p value of 0.004 compared to 0.025), I did not apply this very small significant level because of the logistical issues in accessing such a big sample size and the limited information p value could provide (see below for interpretation), but care should be taken to interpret these findings appropriately. Moreover, the odds ratio was calculated and presented close to p value in the tables, providing more information on the results—the size of the difference of proportions that p value cannot present.

Confounding factors were selected based on the systematic literature review and prior association analysis from which significant association was found with outcome variables. Thus, age, gender, rurality, school, and smoking were included and adjusted in the multivariate logistic regression analysis. The majority of confounding effects could be minimised. However, unmeasured confounding factors (e.g. family income) or unknown ones may still exist and cannot be ruled out.

5.3 Main contributions of my thesis

The main contributions of my thesis can be divided into two categories—contemporary evidence relating to the Chinese population, and methodological considerations for future research. In relation to evidence, four areas of results from my thesis (see below 5.3.1–5.3.4) may contribute to the evidence base; for methodological considerations, I have developed a quality assessment tool and a theory-based questionnaire suitable for use in China.

5.3.1 Systematically synthesising the evidence in Chinese literature

The first contribution of my thesis is in providing synthesised evidence about knowledge of and attitudes towards HPV infection and vaccination from Chinese-language literature. Findings of academic research are mostly reported in English-language peer-reviewed publications, and although some Chinese-language literature is available online, such as CNKI, it cannot be easily understood by international researchers because of the language barrier. Hence, my review provides an important and, I hope, useful contribution to this field by systematically synthesising and presenting the results from the Chinese-language literature and in this way providing detailed evidence from Chinese populations that is largely absent from English-language literature. Variation in the standard of reporting in Chinese academic journals leads to limited and heterogeneous evidence; however, my review is still of importance, as it provides contemporary evidence from Chinese-language literature as well as suggesting potential areas for future research. The findings from my review may have some relevance for those provincial regions and populations that have not yet been included in academic studies, although I recommend that research in these provinces and communities is carried out.

5.3.2 Estimating the awareness and knowledge of HPV and vaccination among school-age Chinese

Based on my understanding of the literature (as outlined in Chapters 1 and 2), as far as I am aware, my survey is one of the first to estimate the awareness and knowledge of HPV infection and of cervical cancer among high-school-age Chinese in North China. Similarly, it is one of the first to examine factors relating to HPV vaccination in a school-age Chinese population, and to examine differences by gender and age (younger and older than 18 years) regarding knowledge of HPV and vaccination in Mainland China. My survey was a localised one, but the results may be generalised to similar populations in selected inland provinces (e.g. Henan) in Mainland China.

5.3.3 Identifying the factors that would facilitate or hinder the acceptability of HPV vaccination in Chinese

Again, according to my understanding of the literature (as outlined in Chapters 1 and 2), my survey is among the first to examine the acceptability of HPV vaccines among a high-school-age Chinese population in Mainland China. It is also among the first to explore the facilitators and barriers to HPV vaccination, based on the behavioural theory of the Health Prediction Model, in this population. Examples include whether the younger generation have perceptions of the importance (risk or severity) of cervical cancer and whether their perceptions of the effectiveness of HPV vaccination might influence their vaccination behaviours. Information on these factors may offer evidence for future cervical cancer prevention programmes.

5.3.4 Identifying the stigma in HPV infection among school-age Chinese in Mainland China

Stigma about HPV infection has been explored in Chinese women in Hong Kong, but to date it had not been reported from Mainland Chinese populations. My survey is among the first to examine stigmatising attitudes towards HPV infection among the younger generation in contemporary Mainland China. I found that although younger generations in my survey population in China are less likely to conform to the traditional social norms (e.g. abstinence before marriage), pressure from peers, parents, and the entire societal environment would still have a great influence on their perceptions and behaviours.

5.3.5 Developing a quality assessment tool to critically appraise observational studies in Chinese literature

I have developed a quality assessment tool for observational studies in Chinese literature, adapted from previously published tools, and my review was the first one I am aware of to assess the quality of Chinese-language studies in the area of knowledge of and attitudes towards HPV and vaccination, based on this refined critical appraisal checklist. The tool may be of use for critical appraisal of observational studies in Chinese literature.

5.3.6 Developing a theory-based questionnaire of knowledge of and attitudes towards HPV and vaccination

I have developed a theory-based questionnaire examining various aspects of knowledge of and attitudes towards HPV infection and vaccination. I used teenager-friendly Chinese language in the questionnaire, and it may be appropriate for use in future surveys examining the understanding and acceptability of HPV vaccination in teenage populations in Mainland China.

5.4 Recommendations for future research

5.4.1 Recommendations for areas of future research

Though the cervical cancer burden (both incidence and mortality) in China is close to the average of high-income countries, the difference between the minimum and maximum age-standardised incidence is much larger - an 8-fold difference has been reported [256]. This may be because of the disparities between geographical regions in China, as well as its diverse populations. However, these reported rates may also be due to the uncertainty of the reliability of estimated rates. Hence, research on how to accurately measure national estimates of incidence and mortality by population and region is needed to offer information for decision making on adopting HPV vaccination.

My review and survey have highlighted the need for more studies looking at facilitators and barriers to HPV vaccination (including the influence of stigma related to HPV infection). My study also suggested further studies are needed in China among potential recipients—teenagers and young adults—in various geographical regions.

Critically, neither my survey nor other studies carried out in China to date have examined the system-level financial constraints for HPV vaccines—the type and coverage of health insurance that participants receive, and how this might influence the affordability of HPV vaccines. Evidence suggests that the reimbursement rate of HPV vaccines by health insurance in countries where the vaccine is not covered by any health insurance was positively associated with acceptability of the vaccine [257]. Thus, further research is required in China on the acceptability and potential uptake of HPV vaccine in relation to health insurance coverage and reimbursement for the vaccine.

As described, my review focused on Chinese-language literature. Ideally, the next step will be to compare and combine results from both Chinese and English literature to obtain greater insights into the factors affecting HPV infection and vaccination, and cervical screening, in China. Similarly, a review of literature from Chinese populations from Mainland China, Hong Kong, and Taiwan may be of interest to researchers and policy makers.

5.4.2 Recommendations on methodological issues

The wide diversity of populations and geographic regions within China creates difficulties in obtaining accurate national estimates of knowledge of and attitudes towards HPV vaccination. Most studies in China were localised ones—many were based in one provincial site—and although a few multi-centre (more than two provincial sites) studies have been carried out in China recently, the potential representativeness of wider populations was not well stated and this requires further exploration. Some provincial regions have not been included in surveys in either Chinese- or English-language literature, and the available evidence would not be sufficient to represent estimates in these areas and thereby guide future HPV vaccination programmes within these regions.

I suggest the use of standardised protocols, rigorous tools for collecting information, and rigorous analysis methods, which may help to obtain reliable and consistent data and facilitate synthesising cumulative evidence, thereby improving the quality of research.

5.5 Considerations for the introduction of HPV vaccination in China

The introduction of HPV vaccination is a complex process, requiring decision making by and involvement of multi-level stakeholders. Some issues need to be considered prior to implementing prevention programmes for cervical cancer (HPV vaccination alone, or a combination of vaccination and screening). Burchett 2012 [258] has identified nine criteria for decision making when adopting new vaccines in a country. I will use the identified criteria as reference to divide the considerations into seven parts (5.6.1-5.6.7) to see what the facilitators or barriers are to the introduction of HPV vaccination. My review and survey may provide some insight in terms of perceptions of cervical cancer and of the effectiveness of HPV vaccination by the public and related considerations. I will also address these issues from global health perspective.

5.5.1 The importance of cervical cancer in China

A number of factors will likely affect the significance placed on cervical cancer prevention (and detection) in China in coming decades. They include: 1) health priority; 2) disease burden; and 3) perceptions of importance in terms of the perceived risk and severity of cervical cancer. I will discuss these three issues in detail in the global context below.

Health priority and disease burden

WHO has recommended Millennium Development Goals (MDGs) [259] regarding global health, which outlined eight health areas that all countries should try to address, especially low- and middle-income countries. These areas are mostly related to high disease burden and serious threat to human health, including child health, immunization, maternal health, infectious disease, etc. [259]. Good progress has been made in these areas during the past decade: however, as the demographic transition is ongoing, the global map of disease is changing and there has been a shift in the disease burden from infectious disease to non-communicable disease (NCDs) in low- and middle-income countries [260].

China is considered to be a middle-income country and has been striving to achieve MDGs according to WHO guidelines over the past couple of decades, particularly with respect to improving child and maternal health, and infectious disease. For example, China has had an established National Immunisation Plan since 2007 [100], currently providing 14 vaccines free of charge: 11 to all children and 3 to susceptible people in the country [100]. However, because of the shift in disease burden towards NCDs and the fact that the majority of poor people live in rural regions, China may have to face a double burden of infectious disease and NCDs. A global report showed that over 70% of poor people worldwide live in middle-income countries rather than low-income countries, and, like other middle-income countries, China may experience a similar situation.

It is unlikely that cervical cancer — ranked in fourth place among NCDs in women in China — will be prioritised as quickly as infectious diseases (such as measles), which pose an immediate, serious physical threat and the potential for a great population impact. Compared to the vaccines included in the national routine immunisation programmes [100], HPV vaccines are the only ones aiming to prevent a non-infectious disease—cervical cancer in adult women, and with oral or anal cancer in adult men. Regarding the potential recipients of HPV vaccination—teenagers—it is a population that has not been included in the national immunisation programmes in China, which may constitute another barrier to implementing vaccination.

Perceptions of the importance of cervical cancer

Findings in my study suggested a low level of perceived risk and severity of cervical cancer among Chinese teenagers and a lack of specialised knowledge of the prevention of cervical cancer among Chinese health professionals. They suggest that at an individual level many people are unaware of the threat of cervical cancer and the importance and possibility of preventing it.

5.5.2 Characteristics of HPV vaccines

There are two main issues: 1) the effectiveness of HPV vaccines; and 2) the safety of HPV vaccines.

Effectiveness of HPV vaccines

Evidence noting that the short-term population impact of HPV vaccines has been demonstrated in Western countries (Australia, the US, New Zealand, Denmark, Germany, and Sweden) in terms of HPV infection, genital warts, and cervical lesions [261]; this was described in Chapter 1. As cancer development may take several decades, the long-term effect of the vaccine remains to be seen. However, two main factors may affect the ability to obtain evidence of the effectiveness of HPV vaccines in China. First, evidence of the short-term effect of HPV vaccines in Western countries may not act as reference for Chinese people because of Chinese regulations. The Chinese State Food and Drug Administration requires external drug companies to perform clinical trials in Mainland China among Mainland Chinese prior to licensing their products. Phase III clinical trials by GSK and Merk had finished in Mainland China by 2013, and two Chinese drug companies are currently carrying out clinical trials[93]. Second, another barrier is the endpoint of the trials in China, which is the precancerous cervical lesions rather than persistent HPV infection - the recommended endpoint from WHO [262]. However, it may take decades to get significant results of precancerous lesions in clinical trials in Mainland Chinese population due to the late start of trials of HPV vaccines in China, although preliminary evidence has been found in Australia [75], Scotland [76] and Denmark [77]. Thus, evidence of the effectiveness of HPV vaccines has not been available in Chinese people according to the Chinese regulations and the endpoint used.

Safety of HPV vaccines

Evidence suggests there was not a significant difference in vaccine-related serious adverse events between the vaccine and control groups [72]. Minor side effects occurred, such as pain and swelling, but this was usually of short duration [72]. Similarly, clinical evidence regarding safety is required to be gathered from Chinese people, according to Chinese regulations.

5.5.3 Vaccine delivery

I will address issues around the delivery of HPV vaccines in the following three parts: 1) age; 2) gender; 3) location of vaccination. As the strategy of vaccination would greatly influence these delivery issues (detailed are described below), the discussion here may offer some information for decision making.

Age

Given the fact that HPV vaccine to those who are already sexually active have not been proved effective and may lead to a waste of resources, people prior to sexual debut are recommended as appropriate recipients for HPV vaccination [4]. A Chinese study has been carried out to estimate the average age of sexual debut and found that 15 years old would be the ideal vaccination age given the estimated age of sexual debut [60, 94]. However, uncertainty about the accuracy of this estimation resulting from the diverse population and large geographical area of China may limit the effectiveness of implementation of HPV vaccination. According to the experiences of Hong Kong and Taiwan, researchers and policy makers need to consider whether it is necessary in China to widen the age-range of potential recipients from teenagers to adults (as has been done Hong Kong and Taiwan) when the vaccine is not free of charge. [248]

Gender

Males were not recommended for HPV vaccination in some Asian countries and regions [245, 247, 248] (described late in this chapter), but many of these countries are not large, and have less diverse populations than China. Thus, researchers and policy makers in China may need to refer to the strategies adopted in other countries, for example, US. The considerations may include whether it is necessary to include males in the vaccination programme in China to achieve a high level of effectiveness when the coverage for girls is not high (e.g. US.). It may also need to consider whether it is necessary and feasible in China to target a high-risk group (men who have sex with men) with the aim of reducing anal or oral cancer.

Location of vaccine delivery

The location of delivery of HPV vaccination in China may depend on who are the intended recipients are and whether the vaccine is free. If it was not free and was offered at the recipient's request, clinic and hospitals might be appropriate sites for delivery. However, if it was free, according to the experience of Asian countries, school-age girls aged 16-18 years (ideally) might be the priority cohort, rather than younger or older age groups and boys. Thus, school-based vaccination programmes might be more accessible and achieve a high uptake more easily than community-based health facilities.

5.5.4 Acceptability of HPV vaccines

The findings of my survey suggest that the acceptability of HPV vaccines is high in school-age Chinese, but results from the systematic review suggest that parental acceptability is lower, at least among health professionals. However, these the generalizability of these findings is limited as these levels of acceptability were not assessed under various scenarios of cost, safety, effectiveness, etc. Hence, I will consider the influential factors in the acceptability of HPV vaccines that were identified in my survey here. They include: 1) perceptions of the effectiveness of HPV vaccines; 2) perceptions of the safety of HPV vaccines; 3) the distrust of drug companies; 4) the stigma of HPV vaccination.

Perceptions of effectiveness of HPV vaccines

The findings of my survey suggested that perceived effectiveness was the second most commonly perceived barrier (over half) among my school-age population, and one study in my systematic review [163] reported that approximately half of health professionals did not believe in the effectiveness of the vaccine. Hence, my findings may suggest that preparatory work is needed prior to implementing HPV vaccination.

Perceptions of the safety of HPV vaccines

The findings of my survey identified the risk of minor side effects as the most common perceived barrier (three-quarters) to HPV vaccination among the school-age young people in my survey population. Females and the older respondents (>=18) were more concerned about the side effects of HPV vaccines. This relatively high level of worry about safety (much higher than neighbouring countries, such as South Korea and Philippines) might be related to the highly publicised adverse events of other vaccines in China in recent years. The most influential was the adverse effects of HBV vaccination in Hunan in 2013 [257]. Two children were reported to have died; later it was confirmed that the deaths were not related to the injection of the HBV vaccine, but anxiety about vaccination among parents hindered them from allowing their children to be vaccinated in the future. If HPV vaccination is first introduced to younger teenagers, parental concern and worries may be significant.

Distrust of drug companies

Only one third of the school-age Chinese young people in my survey trusted drug companies, which was much lower than other countries, such as Philippines (85%) [199]. This low level of trust in drug companies may also be related to the adverse events around vaccination that have occurred in China in the last couple of years (see the example of events surrounding HBV vaccination described above). This distrust may affect the introduction and implementation of HPV vaccines in China, especially when international (e.g. GSK) and national (Chinese) drug companies are marketed roughly at the same time, but are priced differently. Thus, preparatory work and research on this issue are required.

Stigma in relation to HPV vaccination

My survey suggested that stigma might be caused by the fact that HPV vaccines are for a sexually transmitted infection. The most commonly identified stigma in my school-age sample was 'People will gossip about those who get the HPV infection', followed by 'Keep a social distance from those who have got HPV infection'. Furthermore, stigma also existed among males who were more concerned than females that HPV vaccines would lead to people having more sexual partners. However, whether stigma surrounding HPV vaccination would occur in the society as a whole or among a specific population may largely depend on how the government defined the vaccine when it was introduced and how the vaccination campaign was implemented.

To summarise, perceptions of effectiveness and safety, distrust of drug companies, and stigma surrounding HPV vaccination may be barriers to the acceptability of HPV vaccines; however, there are also some facilitators that have a strong influence on the decisions of both recipients and policy makers. Evidence showed technical agencies like WHO and United Nations Children's Fund (UNICEF) play an important role in health promotion [258]. The example of tobacco control in Beijing has demonstrated this. WHO Beijing office has successfully worked together with Beijing Municipal Government to pass a new law, making 'all indoor public places in Beijing 100% smoke-free from 1 June 2015' [264]. Hence, it offers an example of how a health intervention can be introduced in China, one that might provide lessons for the introduction of the HPV vaccination in China.

5.5.5 System issues regarding HPV vaccination

Burchett's 2012 [258] study found that when adopting a new vaccine nationally, high-income countries were more concerned about safety and acceptability issues, and low- and middle-income countries were more likely to examine health system weaknesses and financial constraints. However, these factors might all occur concurrently in China: China has a large geographical area and diverse population and is experiencing both economic and demographic transition and facing issues in both poor and wealthy regions, similar to both low-income and high-income countries in the world. Hence, apart from the acceptability of HPV vaccines, I will also address issues regarding system weaknesses and financial constraints.

System issues

An ideal national cervical cancer prevention programme should have the following components [5, 58] (details stated in Chapter 1, summarised here): 1) primary prevention (e.g. sexual education including condom use, and introduction of HPV vaccination); 2) secondary prevention (cervical screening); 3) a monitoring system, offering sustainable infrastructure to monitor, evaluate, and supervise the vaccination programme. However, there is no primary care system in China, and the already overburdened hospitals in big cities and shortages of gynaecologists and cytologists in rural regions might hinder the introduction of a national vaccination programme. The lack of a national surveillance system and infrastructure for the vaccination of teenagers would be another system-level barrier. Vaccination administration is important to ensure the effectiveness and safety of vaccines; the events surrounding HBV vaccination in Hunan was an example demonstrating the insufficient training for technicians and the lack of infrastructure for monitoring. Hence, prior to the introduction of HPV vaccines, a complete and sustainable system must be established.

Reduction of disparities

If the HPV vaccine is not included in the national immunisation plan free to the whole population in China when it is introduced, health inequalities for HPV vaccine uptake, and ultimately for cervical cancer rates, may emerge. The findings in my study suggested differing levels of knowledge and attitude by age, gender, and rurality, which suggest that future prevention interventions — e.g. raising awareness or skill building — should be tailored to the specific population to increase the acceptability and efficacy of the intervention, thereby reducing the likelihood of disparities emerging. For example, use of teenager-friendly language in the materials of the health education curriculum should be encouraged. Ethnic and social disparity may be introduced by a free but not nationally implemented vaccination strategy - the likely strategy for HPV vaccination in China in the near future. Hence, the needs of underserved populations should be highlighted as well. The findings of my study suggested that these people (e.g. Uyghur and rural people) were more likely to have less knowledge of HPV and cervical cancer, and to be more concerned with cost. Thus, educational intervention may also have to be culturally sensitive, for example, the use of Uyghur-language materials. I listed the potential highlighted population based on the findings of my study; they would include, but not be restricted to: 1) ethnic minority populations; 2) teenagers younger than 18 years old; 3) female students in high school and college; 4) rural residents; 5) teenage children of adult immigrants from rural regions in big cities; 6) teenage immigrants from rural regions in big cities; 7) people living in West China.

5.5.6 Financial constraints

Financial constraints exist at both individual and system levels.

Individual-level

Compared to the safety and effectiveness of HPV vaccines, cost was viewed as less of a perceived barrier by my survey participants. But in my systematic review of the Chinese literature, cost was the most examined issue relating to HPV vaccines. Evidence showed the average affordable out-of-pocket cost of HPV vaccines for the individual was less than $50 for each vaccinated person, which was also viewed as a cost-effective price in China [91]. Hence, based on the affordable out-of-pocket cost by individual Chinese [91], the government would subsidize up to 80% (($300-50)/$300) of the cost if three-dose HPV vaccines were introduced in China at full cost - approximately $300—by GSK or Merck. However, cost would be reduced if a two-dose HPV vaccine was licenced for instead of a three-dose schedule in China.

System-level

At system level, the cost of HPV vaccination should include cost of the vaccine itself and the cost of administration—storage, transport, monitoring, and supervision[265]. From a health economic perspective, the cost described in my survey and review referred to out-of-pocket costs for vaccination, not those covered by health insurance. Until the end of 2014, most eastern Asian countries and regions—Japan, South Korea, Taiwan, etc.—have not included HPV vaccination in their national routine programmes, and the likely recipients have to pay the entire cost on their own [240-242]; situations in these neighbouring countries and regions may greatly influence HPV vaccination implementation in China—probably to a greater extent than those of Western countries. However, if payment for the HPV vaccine was entirely out-of-pocket, it might lead to greater disparities between underserved people and wealthy people.

5.5.7 How might HPV vaccination be introduced in China?

Three main strategies of HPV vaccination exist worldwide [245-248, 266]. They are:
1) national free programmes, adding to national immunisation systems (i.e. UK, Australia, US, Singapore, Malaysia) [84]

2) a national partially subsidised programme, in which recipients pay for a proportion (i.e. France, 35% no reimbursement) [84]
3) a programme not covered by any health insurance (i.e. Hong Kong, Taiwan, Japan, Korea) [267]

So, what would be the most likely approach in China? A few issues should be taken into account; they include the age and gender of the recipients, the delivery venue, and health insurance coverage. The strategies for HPV vaccination in neighbouring countries/regions, which are likely to influence China, are:

- **Malaysia**: free of charge for 13-year-old Malaysian girls since 2010 at schools or clinic; the uptake in 2011 was 87.1% in 13-year-old girls [245].
- **Japan**: offered since 2010 (some regions subsidise the whole cost, while others ask for $500) and the recommended age is 13–16 years; however, from June 2013, the HPV vaccine was no longer recommended by the government due to its side effects [247].
- **South Korea**: licensed in 2007 and recommended for 15–17-year-old girls and 9–15-year-old boys in 2010. It was not covered by national health insurance and was offered for $360 for the completion of three doses [246].
- **Hong Kong:** introduced in 2006, Gardasil was for 9–45-year-old females; Cervix was for 10–45-year-old females. Recipients had to pay $300 for three doses in a private clinic [248].
- **Taiwan:** introduced in 2011**,** Gardasil was for 9–26-year-old females; Cervix was for 10–25-year-old females. Recipients had to pay $350 for three doses in a clinic or hospital [251].
- **Vietnam**: Recipients had to pay $240 for three doses. Cervarix was for 10–25-year-old women, and Gardasil for 9–26 year-old-women [266].

None of these countries have included males in HPV vaccination programmes, and Hong Kong, Taiwan, and Vietnam offered the vaccines for both teenagers and adults. Older adult women have also been recommended for vaccination in Hong Kong.

China seems likely to develop a strategy which is tailored for its own unique circumstances. It is an incredibly diverse country, with distinct geographical regions and racial groups. There are significant financial constraints, and at present there is not a great willingness to roll out a national programme. However, given worldwide trends, it seems likely that such a programme will be introduced at some point in the future—either through a one-off initiative or through incremental change. When this happens, attitudes, knowledge, and practices (such as those demonstrated in my thesis) will have an important influence on implementation. In particular, they highlight the need for appropriate educational and awareness-raising strategies to address knowledge deficits and attitudinal barriers. It is my hope that the findings of my thesis will add to the body of knowledge underpinning these strategies.

List of papers in preparation

I am in the process of preparing two papers from my PhD thesis. Once these are completed I will submit a third, 'overview' paper which synthesises the survey and systematic review and provides commentary on likely implications, in a global context, for implementation of HPV vaccination over the next decade.

1. Wang D, Dozier M, Weller D, Campbell C. Knowledge, attitudes and behaviours towards HPV vaccination in the Chinese population: A systematic review of Chinese literature

Target Journals: Vaccination, PLOS Medicine, American Journal of Public Health

2. Wang D, Li Xiaoxia, Campbell C, Weller D. HPV vaccination and cervical screening in China; Survey on knowledge, attitudes and beliefs amongst schoolchildren in Heilongjiang province.

Target journals: Bulletin of the World Health Organisation, Lancet Global Health, Asia-Pacific Journal of Public Health

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Appendices

Appendix 1: Summary of included studies in the systematic review

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Chen J et al	Zhejiang	2010	123	Urban hospital-based	Telephone interview with HPV positive women at home	17-79	HPV positive women who took the HPV test from March to April in 2010 at one hospital	69.92% of the participants knew about HPV infection and the relationship with cervical cancer; these participants showed panic and anxiety on the results.
Cui B	Liaoning	2010	1160: 660 from 7 urban hospitals,500 from villages	Urban hospital and village-based	Questionnaire filled in at one room in the selected hospitals and villages supervised by the trained researchers	15-59	Outpatients, inpatients and female relatives of the patients in seven urban hospitals; women residents in the selected villages	17.6% urban residents and 17.2% rural residents had heard of HPV; 9.2% urban and 5.8% rural residents knew HPV caused cervical cancer; 8.0% urban and 10.6% rural residents had heard of HPV vaccine; age, education was the factors that influenced the knowledge; 3.8% urban and 2.0% rural residents thought vaccine was targeted to the women who do not have sex before; 68.2% urban and 63.8% rural residents were willing to be vaccinated; safety and efficacy were the barriers of vaccination for urban residents. Rural residents worried about cost and thought they didn't' have the risk for being infected.
Fu FH et al	Beijing	2008	2952	Urban community-based	Interview-administrated questionnaire conducted by the trained researchers	40-95	Women residents in three communities in Shijingshan district from April 7th to 18th in 2008	16.3% of the participants knew about HPV infection, 6.68% know the relationship between HPV and cervical cancer; 65.34% perceived high risk to be infected by HPV.
Fan XF et al	Xinjiang	2011	242	Not available	Questionnaire filled in at the same time at one place by the participants	28-60	Women with low medical insurance	21.9% of the participants knew about HPV as the risk factor for cervical cancer; 25.4% of the participants know HPV can be sexually transmitted; there is significant difference on the knowledge between HPV positive and negative women.

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Fan BJ	Liaoning	2009	962	Urban hospital-based:	Interview-administrated questionnaire conducted by the researchers	19-72	Women outpatients selected from a hospital within one year	23.6% of the participants had heard of HPV; 56.83% of the participants knew HPV can cause cervical cancer; 88.05% of the participants were willing to be vaccinated; safety and source of the vaccine were the main concerns of the vaccine; worrying to be infected by HPV and suffered by genital warts were the reasons for being vaccinated; 55.41% accept the vaccine offered by government; 46.57% expect the government cover all cost.
Feng SW	Zhejiang	2010	1432: 782 women from urban hospitals, 650 women from rural hospitals	Urban and rural hospital-based	Questionnaire filled in at selected hospitals supervised by the researchers	20-50 in urban areas; 22-50 in rural areas	782 women from urban hospitals, 650 women from rural hospitals within six months	39.1% urban and 27.1% rural residents had heard of HPV; 23.7% urban and 15.7% rural residents had heard of HPV vaccine; newspaper and television were the main source of obtaining the knowledge; previous screening history, age, education and economic condition were correlated with the knowledge; 65.4% urban and 57.1% rural residents thought married women should be vaccinated;
Gao L et al	Yunnan	2008	2648	Village-based	Interview-administrated questionnaire conducted by the researchers	30-59	Rural women from Linxiang district in Yunnan province	2.91% of women knew HPV is the cause of cervical cancer.
Guzhanuer A et al	Xinjiang	2008	560	Village-based	Interview-administrated questionnaire conducted by the researchers	Not available	90% Uighur men were from rural regions, 10% Uighur men were from urban regions in Hetian district	0% of men knew HPV, and 0% knew HPV is the cause of cervical cancer. 0% knew HPV vaccine.
Gulinuer A et al	Xinjiang	2006	248	Urban hospital -based	Questionnaire filled in at the selected hospital by the gynaecologists	20-65	Women outpatients between March and June in 2006 at Bozhou hospital in Xinjiang	2.42% of the participants knew about HPV infection; 7.26% of the participants knew the risk factors of cervical cancer; there was no ethnicity difference on the knowledge between Han and Uighur population.

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Guzhalinuer A et al	Xinjiang	2006	400	Urban hospital - based	Questionnaire filled in at five hospitals by the gynaecologists	23-76	Uyghur Cervical cancer patients in five hospitals in Xinjiang	No participants knew about HPV infection; 1.3% of the patients knew the risk factors of cervical cancer.
Huang GF et al	Guangdong	2008	196	Urban hospital - based	Questionnaire filled in at the selected hospital by the participants	20-58	Women during a certain time period at the selected hospital	32.14% of the participants were willing to be vaccinated; aged 30-50 participants were more likely to be vaccinated than aged 20-30 participants.
He M et al	Seven regions of China	2007-2009	9865 women 780 health professionals	Urban hospital-based	Questionnaire filled in at 14 hospitals in seven regions of China by the participants	18-82	Women outpatients and health professionals at 14 hospitals from 2007 to 2009	32.85% women had heard of HPV and 89.62% health professionals knew HPV caused cervical cancer; 72.31% women and 69.77% health professionals were willing to be vaccinated; that the vaccine hasn't been promoted in large scale is the barrier for not being vaccinated; 56.21% women tend to receive the vaccine offered by the government.
He X et al	Henan	2009	2102	College-based	Questionnaire filled in during class supervised by the trained researchers	16-26	1093 female and 1009 male students from two universities in 2010	43.0% students had heard of HPV; 69.2% students knew HPV can be sexually transmitted; female students had less knowledge than male students.
Jiang SY et al	Shanghai	2007-2009	944	Urban community-based	Questionnaire filled in at one place supervised by trained researchers	20-65	Women residents in one community of Hong Kou district of Shanghai city in 2010	34.1% of the participants knew HPV can cause cervical cancer; there was significant difference on the knowledge between screening group and non-screening group.
Lu KN	Beijing	2008	104	Urban hospital-based	Questionnaire filled in at the selected hospitals by the participants	19-69	Outpatients and inpatients selected from 3 hospitals from Sep to Dec in 2007	46.2 of the participants had heard of HPV; 52.9% of the participants knew HPV can cause cervical lesions;
Li J et al	Beijing	2008	1013	Urban community-based	Interview-administrated questionnaire conducted by the trained researchers	15-54	Women residents in Zhanlanlu community of Beijing city from June of 2006 to June of 2007	30.7% of the participants had heard of HPV, 51.78% of them knew HPV was related to cervical cancer; 75.91% of the participants were willing to be vaccinated; that the vaccine hasn't been promoted in large scale is the barrier for not being vaccinated; 55.77% participants tend to receive the vaccine offered by the government.

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Li JM et al	Guangdong	2008	304	Urban community-based	Questionnaire filled in at one place in the community by the participants	18-60	Women residents in one community in Baoan district of Shenzhen city	30.9% of the participants knew HPV causes cervical cancer; 54.9% of the participants knew HPV can be sexually transmitted; there was significant difference on knowledge of HPV between screening women and non-screening women.
Li XP et al	Zhejiang	2007	300	Urban community-based	Questionnaire filled in at one place supervised by the trained researchers	20-50	Women residents in Nanpu community of Wenzhou city	7.5% of the participants had heard of HPV; 11.5% knew HPV can be sexually transmitted; 13% knew HPV causes genital warts; 21.5% knew that HPV can cause cervical cancer; the knowledge increased after health promotion intervention
Li J	Liaoning	2011	160	Urban and rural hospital-based	Questionnaire filled in at one place	36.6±9.6	Doctors and government officials	88.8% and 78.8% doctors had heard of HPV and knew HPV is the cause of cervical cancer, so did 43.8% and 30% government officials; 51.3% doctors and 27.5% officials had heard of HPV vaccine; over half of them thought CDC should be the vaccination centre; 12.5% doctors and 5% officials thought women who never had sex before would be the target population for the vaccines; 81.3% doctors and 73.8% officials would like to be vaccinated; 78.8% doctors and 81.3% officials would like their daughter to be vaccinated;
Li CT et al	Xinjiang	2011	960	Not available	Questionnaire filled by the participants themselves	20-39	Women residents in Tianshan district in Urumqi city	11.0% of women knew about HPV. 58.9% of women said they would wait to be vaccinated until others get the vaccine; 33.3% won't take vaccine now; 89.3-100% thought the efficacy and safety is most important; 47.9% thought the protection time is important; 89.0% can't accept 3000 yuan for vaccination; 62.3% would accept imported vaccines; 44.3% agree to vaccinate their daughter;

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Liu ZH et al	Hunan	2011	848: 396 male and 452 female students	High school-based	Questionnaire filled in during class	14-18	High school male and female students in Xiangtan city	10.1% had heard of HPV; 9.1% had heard of HPV vaccine; 18.6% knew HPV causes cervical cancer; 16.3% knew HPV is sexually transmitted; 20.9% knew men can also infected with HPV; the knowledge were mostly from TV& radio(59.3%), internet(57.0%), rarely from parents(25.6%), health professionals(20.9%); those with good school performance had higher knowledge of HPV.
Long XE et al	Zhejiang	Not available	286	College-based	Questionnaire filled in during class supervised by the trained researchers	>18	Medical testing major students from selected college	74.2% junior students, 21.9% sophomore and 3% freshmen had heard of HPV; 81% of them knew HPV can be sexually transmitted; 10.9% had heard of HPV vaccine.
Ma D et al	Hebei	2011	198	Urban hospital-based	Questionnaire filled in at the selected hospital	20-54	49 doctors and 149 nurses from selected hospital in Tangshan city	91.8% doctors and 77.2% nurses had heard of HPV; 87.8% doctors and 67.1% nurses knew HPV is sexually transmitted; 81.6% doctors and 50.3% nurses knew persistently infected with high-risk HPV is the cause of cervical cancer; 53.1% doctors and 38.9% nurses knew HPV 16/18 is related to cervical cancer; 18.4% doctors and 12.1% nurses knew HPV infection could be cleared spontaneously; 53.1% doctors and 44.3% nurses had heard of HPV vaccine; 59.6-65.8% them worried about the safety and efficacy; over 70% them thought both men and women should be vaccinated; 36.7% doctors and 47.0% nurses thought HPV vaccine would increase high-risk sexual behaviour; over 65% of them thought government should pay for the vaccine; 90% of them would like to pay less than 200 yuan; 23.4% doctors and 34.8% nurses would like to be vaccinated; over 55% of them suggested the target population should be people over 18 years; less than half of them suggested HPV vaccine as routine vaccine in China;

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Ma D et al	Beijing	2010	249: 100 community women and 149 women outpatients	Urban community and hospital-based	Questionnaire filled in at one place supervised by trained researchers	30-55 community; 16-56 outpatients	Women residents from a selected community and women outpatients from a selected hospital	33% of the community women knew HPV causes cervical cancer and so did 24.2% of women in the hospital; 29% of the community women knew that HPV can be sexually transmitted and so did 14.8% of women in the hospital.
Ren CL et al	Xinjiang	2010	1005	Not available	Interview-administered questionnaire by researcher	18-58	Han, Uighur and Hui women were equally distributed	20.6% Han, 5.2% Uighur and 11.5% Hui knew HPV is the cause of cervical cancer, and there is significant difference among different ethnicities; 13.8% Han, 2.4% Uighur and 3.4% Hui knew condom could prevent HPV infection.
Song D	Shanxi	2007	957	Village-based	Questionnaire filled in at selected villages by the participants	15-54	Women from 26 villages in Xiangyuan county in Shanxi province	5.9% of the participants had heard of HPV; 34.61% of the participants knew HPV can cause cervical cancer; 96.5% of the participants were willing to be vaccinated; source and safety of the vaccine were the main concerns; 60.7% of the participants accept the vaccine offered by large medical companies; 67.2% expect the government covered all the cost the vaccine;
Sun J	Liaoning	2010	310	Urban hospital-based	Questionnaire filled in at selected hospital by the participants	21-60	Women from one hospital in Dalian from Feb to Mar in 2010	23.9% of the participants knew HPV can cause cervical cancer; 20.3% of the participants knew HPV can be sexually transmitted;
Shi YY	Heilongjiang	2010	1200: 600 village women and 600 women outpatients	Village and urban hospital-based	Questionnaire filled in by health professional researchers	20-60	Women residents from three selected villages and women outpatients from a selected hospital	13.3% of the participants knew HPV causes cervical cancer.
Wang HQ et al	Hebei	2011	257	Urban hospital-based	Questionnaire filled in at the four selected hospitals	20-53	Obstetricians and Gynaecologists from four hospitals in Tangshan city	92.2% had heard of HPV, knew that HPV can be sexually transmitted; 34.3% knew HPV infection can be cleared automatically; 83.7% of the participants knew HPV causes cervical cancer; 34.2% of the participants had heard of HPV vaccine; 67.3% concerned about the safety of the vaccine

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Wen LZ et al	Xinjiang	2009	400	Urban hospital-based	Questionnaire filled in at the selected hospital by the participants	22-48	Women outpatients at one hospital selected from Jan to June in 2009	45% of the participants had heard of HPV; 30% of the participants knew HPV was related to cervical cancer; 7.5% of the participants had heard of HPV vaccine; The knowledge increased after health promotion intervention.
Wang QL et al	Sichuan	2010	886	Village-based	Interview-administrated questionnaire conducted by the trained researchers	41.9 (mean)	Women residents from 3 counties in north Sichuan mountain areas	0.2% of the participants knew the relationship between HPV and cervical cancer.
Wu Y	Zhejiang	2010	489	Not available	Questionnaire filled in at one place by the participants	>15	Women residents in Hangzhou city	28.83% of the participants had heard of HPV; 47.85% of the participants were willing to be vaccinated; 82% of the participants accepted the vaccine offered by the government; concerned about the source of the vaccine and side effect were the barriers.
Wang XM et al	Shanxi	2010	2269	Urban hospital-based and village-based	Interview-administered questionnaire by researcher	25-73	341 urban women residents and 1928 rural women residents	50.7% urban residents and 34.6% rural residents would like to pay for some amount of the price of the vaccine; around 60% of them would like to pay less than 100 yuan;
Xiamixinuer A et al	Xinjiang	2004-2006	245	Urban hospital-based	Questionnaire filled in at the selected hospitals by the gynaecologists	23-85	Uighur cervical cancer patients selected from five hospitals from Jan of 2004 to Jul of 2006	No participants had heard of HPV or HPV vaccines, knew HPV causes cervical cancer, and knew HPV can be sexually transmitted.
Xiao W et al	Beijing	2008	368	Urban hospital-based	Questionnaire filled in at the selected hospital by the participants	21-74	Women outpatients selected from one hospital from Jan to Apr in 2008	45.81% of the participants had heard of HPV; 72.75% of the participants were willing to be vaccinated; the barrier are that they didn’t perceive the risk to be HPV infected and worried the vaccine hasn’t been promoted in large scale; 70.97% of the participants tend to accept the vaccine offered by the government; 61.51% would take the vaccine from the recommendation of doctors

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Xing YX et al	Qinghai	2009	200	Not available	Questionnaire filled in by local doctors	18-63	136 Tibetan women residents and 64 Han women population	1.56% Han and 2.2% Tibetan had heard of HPV; the knowledge increase with the increased level of education;
Xu CY et al	Beijing	2007-2008	6339	Urban and rural community-based	Questionnaire filled in at one place supervised by researchers	25-54	Women residents from four districts of city, four districts of inner suburbs and four districts of outer suburbs	26.9% of the participants knew that HPV is the risk factor of cervical cancer
Xu LN et al	Beijing, Tianjin, Shanxi	2009	1666: 640 urban residents and 1026 rural residents	Urban hospital and village-based	Questionnaire filled in at one place supervised by the trained researchers	15-59	640 urban women residents from selected hospitals and 1026 rural women from selected villages from Jun to Nov in 2009	19.87% of the participants had heard of HPV; 62.84% of the participants knew HPV causes cervical cancer; urban residents had better knowledge than rural residents; 15.43% of the participants had heard of HPV vaccine; 76.71% of the participants were willing to be vaccinated
Xie Y et al	Sichuan	2010	2000	Village-based	Interview-administrated questionnaire conducted by trained researchers	30-59	Women residents from 3 counties in August in 2010	0.8% of the participants had heard of HPV.
Ye JR et al	Guangdong	2010	1120	Village-based	Questionnaire filled in at one place	23-51	560 married women from two villages	3.7% knew HPV; 3.2% knew HPV is related to cervical cancer;2.6% knew HPV vaccine;
Zhang LJ et al	Guangdong	2006-2007	100	Urban hospital-based	Questionnaire filled in at the selected hospital by the participants	18-54	Women patients selected from one hospital from Dec of 2006 to Sep of 2007	28% of the participants knew the mode of transmission of HPV; 11% of the participants knew the relationship between HPV and cervical cancer; the knowledge increased after health promotion intervention.

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Zhao DJ et al	Shanghai	2009	997	Urban community-based	Questionnaire filled in at one place supervised by the trained researchers	16-54	Women residents in two selected communities in Shanghai	20.6% of the participants had heard of HPV; age, education, profession were the factors that influenced the awareness; 66.1% of the participants were willing to be vaccinated; 53.64% of the participants would like their daughter to be vaccinated; the barriers were that participants didn't perceive the risk of being infected, the vaccine hasn't been promoted in large scale, concerned about the source of the vaccine. 65% receive the vaccine offered by the government.
Zhou JY et al	Beijing	2008	2000: 619 urban residents and 1381 rural residents	Urban and rural community-based	Questionnaire filled in at one place supervised by the trained researchers	30-59	Women residents in the both urban and rural communities from Apr to Dec in 2008	15.8% of the participants knew that HPV infection causes cervical cancer.
Zhou LX et al	Guangdong	2010	752: 371 community women and 381 women outpatients	Urban community and hospital-based	Interview-administrated questionnaire conducted by trained researchers	16-55	Women residents from selected community and women outpatients from selected hospital	There was difference between women selected from community and hospital on the awareness of HPV, HPV vaccine; they were 36.12%, 12.13% of community women and 46.46%, 22.57% of hospital women. Knowledge of HPV causes cervical cancer was significantly different, 14.28% of community women and 27.82% of hospital women.
Zhou Y et al	Hunan	2009	207: 64 male and 143 female students	College-based	Questionnaire filled in during class	17-21	Fresh students from the selected college	17.87% of the participants had heard of HPV; 62.16% of the participants knew HPV infection can be asymptomatic; 29.73% knew HPV can be sexually transmitted; 86.49% knew HPV may lead to cervical cancer.
Zhou Y et al	Hunan	2009	2293: 1428 male and 865 female students	College-based	Questionnaire filled in the dormitory	17-25	Students from selected college	20.5% males and 17.0% females had heard of HPV, there is significant difference between males and females; senior students knew more about HPV than other grades; TV, radio and magazines are the main source (74.1%) of HPV information, internet is another important source (17.2%); students rarely get HPV information from friends (4.1%) and families (3.0%);

Study	Study location	Year of study	Number of participants	Study setting	Study instrument	Age (years)	Study population	Main result
Zhou Y et al	Shanxi	2010	500	Village-based	Interview-administrated questionnaire conducted by the trained researchers	17-59	Women residents in the selected county in Shanxi province	11.8% of the participants had heard of HPV; age, education, profession were the factors that influenced the awareness; 69.5% knew HPV may cause cervical cancer, 40.7% knew HPV may cause genital warts; 25% had heard of HPV vaccine; 82% would like to be vaccinated; cost, safety were the main barriers.

Appendix 2: summary of excluded studies in the systematic review

Study	Title	Exclusion reasons
Ao MH	Research and Evaluation of Opportunistic Cervical Cancer Screening	Knowledge, attitudes and acceptance are not discussed
Bao LH et al	The risk factors and prevention of cervical cancer	It's a general review
Cui LQ	The clinical analysis of 53 cervical cancer women	Knowledge, attitudes and acceptance are not discussed
Cheng HE	HPV -16 E6 gene expression study on cervical cancer CaSki cell	Knowledge, attitudes and acceptance are not discussed
Cao YH	A study of etiology and determinants of cervicitis	Knowledge, attitudes and acceptance are not discussed
Cao SD	The study on the mechanism of thrombin-induced nausea conversion of human bronchial epithelial cells	Knowledge, attitudes and acceptance are not discussed
Cao JP et al	health education of patients with condyloma	It's a general review
Chen BC et al	Antiviral drug and its intellectual property rights in China	It's a general review
Chen S et al	Treatment and nursing of condyloma acuminata with pregnancy	Knowledge, attitudes and acceptance are not discussed
Cui F et al	The relationship between HPV subtypes and cervical lesions among women in Hongkou district in Shanghai	Knowledge, attitudes and acceptance are not discussed
Cheng SX	The relationship between high risk HPV infection in cervical cancer and p16, PTEN protein expression	Knowledge, attitudes and acceptance are not discussed
Cheng YX et al	Therapeutic Effect of Herbal Compound Including Arsenic and Its Effect on Human Papilloma Virus Load in Patients with Chronic cervicitis	Knowledge, attitudes and acceptance are not discussed
Chen HB et al	HPV infection and relationship with Cervical epithelial hyperplasia	Knowledge, attitudes and acceptance are not discussed
Chen GD et al	The application value of high risk HPV DNA detection in the high-grade cervical squamous intraepithelial lesions screening and follow-up treatment	Knowledge, attitudes and acceptance are not discussed
Chen JX et al	A study on the diagnosis significance of direct immunofluorescence on Condyloma Acuminatum	Knowledge, attitudes and acceptance are not discussed
Chen RL	The expression of PIK3CA gene in cervical lesions and the relationship with HPV infection	Knowledge, attitudes and acceptance are not discussed
Chen SZ et al	Screening of cervical cancer associated genes and bioinformatic analysis	Knowledge, attitudes and acceptance are not discussed
Chen YN	The relationship between PCNA, COX-2 and Cervical squamous cell carcinoma Microvessel density	Knowledge, attitudes and acceptance are not discussed
Chen Q	Preparation on RBC blood group monoclonal antibodies and genetically engineered antibody	Knowledge, attitudes and acceptance are not discussed
Dai ZL et al	Study on the correlation between HPV and cervical cancer early lesions	Knowledge, attitudes and acceptance are not discussed
Du LB	Glucocorticoid induces chemoresistance by modulating the regulatory pathway involved E6, P53 and miR-145 in cervical cancer	Knowledge, attitudes and acceptance are not discussed
Ding HF	The relationship between Keratoacanthoma and HPV	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Ding GC	Detection of Human Papillomavirus in Single Esophageal and Gastric Cardia Cancer and Concurrent Esophageal and Gastric Cardia Cancers from the Same Patient and Studies on Alternations of p53, p16, p21~(WAF1), MDM2 at High-incidence Area in Henan	Knowledge, attitudes and acceptance are not discussed
Fan JN et al	Study on high risk HPV DNA detection and cytology test among rural women in Haiyang	Knowledge, attitudes and acceptance are not discussed
Fei HL	An Evaluation of Five Screening Methods for the Early Detection of Cervical Neoplasia and Cervical Cancer	Knowledge, attitudes and acceptance are not discussed
Fang J et al	The implication of cervical abnormal cytology in pregnancies outcomes	Knowledge, attitudes and acceptance are not discussed
Feng YL	Analysis of Cervical Cancer Screening among Women in XingHuaLing District, TaiYuan, ShanXi Province	Can't extract information on knowledge, attitude and acceptance
Feng SW et al	The application of partnership-based health education in the first visit of Cervical intraepithelial neoplasia patients	Knowledge, attitudes and acceptance are not discussed
Guan WW et al	Analysis the psychological state and nursing strategy of newly diagnosed HPV positive outpatients	Knowledge, attitudes and acceptance are not discussed
Gao K et al	The application of VIA in screening of cervical disease among women workers	Knowledge, attitudes and acceptance are not discussed
Gu Xiaofen	A survey on cervical cancer screening and KAP situation	Can't extract information on knowledge, attitude and acceptance
Guo XQ et al	The discovery of HIV and its great significance	It's a general review
Guo Y	The Association between Epithelial Proliferation and Intraepithelial Infiltrating Inflammatory Cells and the Detection of HPV Infection in Esophageal Carcinoma High-risk Population	Knowledge, attitudes and acceptance are not discussed
Gao D	Epidemiological Features of Warts in Patients from Shenyang, and Clinical Observation on the Effect of Local Thermotherapy	Knowledge, attitudes and acceptance are not discussed
Gao SJ et al	Retrospective analysis of High-grade squamous intraepithelial lesions and Microinvasive Loop electrosurgical excision procedure	Knowledge, attitudes and acceptance are not discussed
Gao N	Mechanism of Boningmycin on anti-tumor and anti-human papillomavirus	Knowledge, attitudes and acceptance are not discussed
Huang JY	The association between XRCC1, MGMT SNP and cervical cancer susceptibility	Knowledge, attitudes and acceptance are not discussed
Huang HS	Woman s and Doctor s Knowledge, Attitudes and Beliefs about HPV Vaccination in Macau	Not in mainland China
Hao XG	The Epidemiological Investigation of Condyloma in Chang Zhi Area	Knowledge, attitudes and acceptance are not discussed
Hu YJ	HPV type detection by Pyrosequencing and HPV 16 Methylation status and cervical cancer-causing effect	Knowledge, attitudes and acceptance are not discussed
He L	The Application of Rapid Pathologic Examination in the Diagnosis and Treatment of Cervical Lesions	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Hu SY	Research on etiology and prevention and control of cervical cancer	Knowledge, attitudes and acceptance are not discussed
Jin YC	The expression of HPV, NFKB in Ovarian cancer tissues and relationship study	Knowledge, attitudes and acceptance are not discussed
Jin W	Clinical observation of Treatment of recurrent genital warts by autologous warts embedded combined topical imiquimod method	Knowledge, attitudes and acceptance are not discussed
JanM A et al	Price is not the only obstacle	Not a research report
Jiang R	The clinical test study on Nakejia treating in high-risk HPV infection	Knowledge, attitudes and acceptance are not discussed
Jiang XM	A Study on the Relationship between hr HPV, L1 Protein, p16 Protein and Cervical Lesions and Their Diagnostic Value in Clinic	Knowledge, attitudes and acceptance are not discussed
Kong Y	The expression of hTERC gene and HPV types and the clinical application	Knowledge, attitudes and acceptance are not discussed
Kong L	Functional research on RbSp48 of HPV caused cervical cancer	Knowledge, attitudes and acceptance are not discussed
Liang YM	The review of human finger length ratio	It’s a general review
Liang XN et al	The clinical value of high risk HPV Auxiliary liquid-based thin-film cytology in cervical screening	Knowledge, attitudes and acceptance are not discussed
Liu J	Studies on regulating roles of Hes1/Hes5 and their signal pathway in cerivical carcinoma cell differentiation	Knowledge, attitudes and acceptance are not discussed
Li YY	Geographic analysis on HPV 58 type	Knowledge, attitudes and acceptance are not discussed
Liu YZ	Study on white lesions of vulva lesions cyclin D1, CDK4, p21 and Cell proliferation index and the clinical observation of Chinese traditional medicine	Knowledge, attitudes and acceptance are not discussed
Liu ZH et al	Study on the health promotion and information need of HPV infection	It’s a general review
Liu KJ	Epidemiology and molecular biology study of risk factors on Uigur and Han cervical cancer in Xinjiang	Knowledge, attitudes and acceptance are not discussed
Liu XT	The information analysis in the tumor vaccine area	Knowledge, attitudes and acceptance are not discussed
Liu X	The expression of human harf-wing gene and HPV in cervical cancer and cervical intraepithelial neoplasia	Knowledge, attitudes and acceptance are not discussed
Liu R	HBC and HPV16L1 carrier influenza generic vaccine research	Knowledge, attitudes and acceptance are not discussed
Liu AL	Stady on the Clinical Application of TERC Amplification of the Exfoliated Cervical Epithelial Cells Detected by FISH	Knowledge, attitudes and acceptance are not discussed
Li XL	Relationship among HPV Infection, FHIT Deletion and Lung Cancer in Nonsmoking Female	Knowledge, attitudes and acceptance are not discussed
Lin CL et al	High risk HPV detection in Cervical intraepithelial neoplasia and cervical cancer screening	Knowledge, attitudes and acceptance are not discussed
Lin YF	A Research on Safety Strategies of Chinese Biotechnology Medicines	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Lin WY	The Application of Modified Reid s Colposcopic Index on Screening of Cervical Neoplasia	Knowledge, attitudes and acceptance are not discussed
Liang JN et al	The clinical value of high risk HPV aided Liquid-based thin-film cytology in the cervical screening	Knowledge, attitudes and acceptance are not discussed
Lu XF	The expression and implication of hWAPL gene in cervical intraepithelial neoplasia and Cervical squamous cell carcinoma	Knowledge, attitudes and acceptance are not discussed
Lv LL et al	The relationship between infection and cervical cancer	Knowledge, attitudes and acceptance are not discussed
Lv FB et al	The diagnosis value of TCT correlated with Electronic colposcopy in the cervical lesions	Knowledge, attitudes and acceptance are not discussed
Lu MG et al	HIV interpretation	It's not a research report
Li SH et al	The analysis of female sexual transmitted disease test results	Knowledge, attitudes and acceptance are not discussed
Luo WM et al	Clinical research of TCT, colposcopy for early stage cervical cancer screening in the primary hospital	Knowledge, attitudes and acceptance are not discussed
Li L et al	The application of HPV self-sampling in the cervical cancer screening	Knowledge, attitudes and acceptance are not discussed
Li RZ et al	Early detection and treatment on cervical screening	Knowledge, attitudes and acceptance are not discussed
Li XD et al	The effect of Local hyperthermia on HPV infection in Epidermis Langerhans cell function activity	Knowledge, attitudes and acceptance are not discussed
Li YB	Study on Commercial sex workers' sexually transmitted infections and related risk factors	Knowledge, attitudes and acceptance are not discussed
Li L	The clinical analysis of Cervical cytology of atypical glandular cells and the correlation with HPV detection	Knowledge, attitudes and acceptance are not discussed
Li L et al	The diagnostic value of atypical glandular cells with other conditions for adenocarcinoma in situ	Knowledge, attitudes and acceptance are not discussed
Li XJ et al	A clinical research on high-risk HPV-DNA testing in screening of cervical disease	Knowledge, attitudes and acceptance are not discussed
Li Y	The correlation research on HPV infection and cervical lesions	Knowledge, attitudes and acceptance are not discussed
Li L et al	Research progress on the HPV vaccine awareness and acceptance in the world	It's a general review
Li Q et al	Study on the way of cervical cancer screening in urban community of China	Knowledge, attitudes and acceptance are not discussed
Li RK	Effect of Sevoflurane with Propofol on Stress Response during One Lung-ventilation	Knowledge, attitudes and acceptance are not discussed
Lu Q et al	A Study on Human Paplillowmarivus Infection Rate of Suscepitble Person in Shenzhen	Knowledge, attitudes and acceptance are not discussed
Lu MG	HIV interpretation for the College Entrance Examination	Not a research report
Liu HM et al	2341 pregnancy women cervical screening and postpartum follow up	Knowledge, attitudes and acceptance are not discussed
Liu H et al	High risk HPV infection of retired women in Gaoqiao community	Knowledge, attitudes and acceptance are not discussed
Liu YJ	The expression pattern of P16INK4a, Ki67 in Cervical intraepithelial lesions and the correlation with HPV infection	Knowledge, attitudes and acceptance are not discussed
Liu C et al	The study on podophyllotoxin Solid Lipid Nanoparticles Transdermal drug delivery agents	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Liu Q	The study on anti-inflammatory effects of vaginal contraceptive suppository	Knowledge, attitudes and acceptance are not discussed
Liu CY et al	Study on cervical cancer screening by high risk HPV second-generation Hybrid Capture test	Knowledge, attitudes and acceptance are not discussed
Min QH et al	Evaluation of Liquid-based Thin-layer Cytological Test and HPV21 Subtype Gene Detection for Cervical Cancer Screening Using ROC Curve Analysis	Knowledge, attitudes and acceptance are not discussed
Nan Y	The TSPAN-1 protein expression and relationship with Ki-67 and CD105 in Cervical squamous cell carcinoma	Knowledge, attitudes and acceptance are not discussed
Pruitt SL et al	Knowledge of cervical dysplasia and human papillomavirus among women seen in a colposcopy clinic	Can't extract information on knowledge, attitudes and acceptance
Pu HO et al	The diagnostic value of Colposcopy of cytology and tumor inherent fluorescence diagnostic apparatus on cervical lesions	Knowledge, attitudes and acceptance are not discussed
Qiao WJ et al	Relevant factors analysis of HPV infection among women	Knowledge, attitudes and acceptance are not discussed
Qiu ZL et al	Analysis of children genital warts infection	Knowledge, attitudes and acceptance are not discussed
Ren CL	Difference and cluster analysis of uterine cervix cancer gene expression profiling of Uygur	Knowledge, attitudes and acceptance are not discussed
Sun P	Relationship between Nasal inverted papilloma and human papillomavirus subtypes	Knowledge, attitudes and acceptance are not discussed
Shi XM	The clinical significance of the serum C-reactive protein in patienst with Lung cancer	Knowledge, attitudes and acceptance are not discussed
Shi YY	The relationship between high-risk HPV infection and cervical lesions	
Shi JF	The epidemiological research on HPV infection and cervical cancer on Shenzhen women	Knowledge, attitudes and acceptance are not discussed
Su S	The expression and implication of Sfrp-1, Wnt-1 gene in cervical cancer and Precancerous lesions	Knowledge, attitudes and acceptance are not discussed
Su YY	The expression of RASSF1A gene and HPV 16 infection in cervical lesions	Knowledge, attitudes and acceptance are not discussed
Sun XP	Local hyperthermia efficacy in common warts of hand and foot	Knowledge, attitudes and acceptance are not discussed
Sun ZH	Psychological Research on Women Infected Genital Human Papillomavirus	Knowledge, attitudes and acceptance are not discussed
Sun HL	Clinical Significance of HPV Test in Examination of Cervical Diseases	Knowledge, attitudes and acceptance are not discussed
Shen H	Epidemiological Studies of AIDS among STD Clinic Attendants and Sex Workers in Jiading District	Knowledge, attitudes and acceptance are not discussed
Shi J et al	Looking for the ultimate invisible culprit	It's not a research report
Shu YH et al	Acetate experiments for the screening of cervical lesions	Knowledge, attitudes and acceptance are not discussed
Song XR et al	HPV and cervical cancer	It's a general review
Song JM et al	HPV 16 L1 Gene Immunization Evaluation and Comparative Study of different immunization schemes and ways	Knowledge, attitudes and acceptance are not discussed
Song CL	Study on FHIT gene Microsatellite instability and Mismatch repair genes expression	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Song YR et al	Etiological factors in younger patients with cervical carcinoma	Knowledge, attitudes and acceptance are not discussed
Sui S et al	The application and significance of opportunistic screening for cervical cancer	Knowledge, attitudes and acceptance are not discussed
Shen YH et al	Study on HPV infection of cervical cancer high incidence rate region in Shanxi	Knowledge, attitudes and acceptance are not discussed
Shen H et al	A Study on HIV,HSV-2,HPV,Syphilis and Risk Factors Among STD Clinic Attendants in Jiading District,Shanghai	Knowledge, attitudes and acceptance are not discussed
Tang YF et al	The evaluation of cervical LEEP biopsy correlated with HPV 16,18 and TCT testing for CIN1	Knowledge, attitudes and acceptance are not discussed
Tong XJ et al	The correlation study on high risk HPV infection and cervical lesions	Knowledge, attitudes and acceptance are not discussed
Wang W et al	Impact of HPV infection on adolescent and young adult women	It's a general review
Wang J et al	HPV types distribution and study on gene chip technology in cervical screening	
Wang SM et al	Controlled Research on Mental Intervention Effects for the HPV Positive Patients	Knowledge, attitudes and acceptance are not discussed
Wang DL et al	Analysis of cervical cancer screening among 4866 rural women	Knowledge, attitudes and acceptance are not discussed
Wang SM et al	Control study on HPV-positive patients with psychological intervention	Knowledge, attitudes and acceptance are not discussed
Wang QX et al	Clinical Consideration in Analysis and Management on Atypical Glandular Cells of Cervical Cytology	Knowledge, attitudes and acceptance are not discussed
Wang CH et al	The implementation of cervical cancer health education on childbearing age women	Knowledge, attitudes and acceptance are not discussed
Wang DH et al	How can people stay away from cervical cancer	It's not a research report
Wang JD et al	Analysis on cervical cytology ASC-US patients and influencing factors	Knowledge, attitudes and acceptance are not discussed
Wang Y	Study on the Vaginal Microflora and the Associated Disease by PCR-DGGE	Knowledge, attitudes and acceptance are not discussed
Wang Q	Value of Visual Inspection with Acetic Acid and Logu s Iodine on Primary Screening for Cervical Cancer and Its Precancerous Lesions	Knowledge, attitudes and acceptance are not discussed
Wang Q	The correlation research on HPV infection and CIN	Knowledge, attitudes and acceptance are not discussed
Wang BZ	New discovering on the secretory form and transporting route of phlypeptide hormones of pancreatic islets and its relationship to type2 diabet4ew mellitus	Knowledge, attitudes and acceptance are not discussed
Wang XQ	Effects o flocal hyperthermia on promoting apoptosis and proinflammatory cytokines of HPV infected keratinocytes	Knowledge, attitudes and acceptance are not discussed
Wang XW	Roles of HPV infection in P53, PCNA in Laryngeal carcinoma	Knowledge, attitudes and acceptance are not discussed
Wang L	Studies on B-sitosterol inhibit Cervical cancer SiHa cell lines and mechanism	Knowledge, attitudes and acceptance are not discussed
Wu RF et al	HPV infection and CIN prevalence among different professional women in Shenzhen	Knowledge, attitudes and acceptance are not discussed
Wu RF et al	The prevalence of HPV infection and Cervical intraepithelial neoplasia and the evaluation of cervical cancer screening	Knowledge, attitudes and acceptance are not discussed
Wu KH et al	Molecular epidemiological analysis of women HPV infection in Guangzhou	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Wu YP et al	Roles of liquid-based cytology and/or HPV DNA test in cervical cancer screening	Knowledge, attitudes and acceptance are not discussed
Wu YZ et al	Review of the therapeutic vaccine	It's a general review
Wu JP et al	The analysis of 8463 cases of cervical cancer	Knowledge, attitudes and acceptance are not discussed
Wu GZ	Mutation Site Analysis of Telomerase Inhibitor PinX1 Gene in Cervical Carcinomaand the Effects of HPV16E6 on PinX1	Knowledge, attitudes and acceptance are not discussed
Wu YZ et al	Review of the therapeutic vaccine	It's a general review
Wu C et al	The clinical analysis of Resection margin status by Cervical loop electrosurgical excision procedure	Knowledge, attitudes and acceptance are not discussed
Wu XJ	The gene expression and the implication of KCC1 upgraded by IGF-2 through Erk1/2 MAPK and PI3K/AKT gene in cervical cancer cell	Knowledge, attitudes and acceptance are not discussed
Wu XY	Women hrHPV infection and relationship between virus and cervical lesions	Knowledge, attitudes and acceptance are not discussed
Wu LJ	Expression of Fhit Protein and Its Correlation with Human Papillomavirus Infection in Cervical Lesions	Knowledge, attitudes and acceptance are not discussed
Xu ZL	The expression and clinical significance of the CD105 in cervical cancer serum and tissue	Knowledge, attitudes and acceptance are not discussed
Xiao W	HPV infection and cervical cancer development study	Knowledge, attitudes and acceptance are not discussed
Xiao B	Six errors sexual attitudes	It's not a research report
Xin WJ et al	Optical system design of Human blood and tissue cell analyzer	Knowledge, attitudes and acceptance are not discussed
Xue JY	Preliminary optimization of the HPV virus particle vaccine preparation process	Knowledge, attitudes and acceptance are not discussed
Ye J et al	HPV epidemiological investigation and the role of cervical cancer risk factors in the HPV screening	Knowledge, attitudes and acceptance are not discussed
Yu JM et al	Analysis of female cervical lesions TCT and TBS detection in Meicheng area.	Knowledge, attitudes and acceptance are not discussed
You XR et al	Clinical analysis of 968 cases of cervical diseases	Knowledge, attitudes and acceptance are not discussed
Yu LM et al	Study on cervical cancer risk factors	Knowledge, attitudes and acceptance are not discussed
Yu LM et al	The analysis of cervical cancer etiology and the trend of young age	Knowledge, attitudes and acceptance are not discussed
Yu HR et al	The establishment of the virus carcinogenic doctrine	Knowledge, attitudes and acceptance are not discussed
Yao YQ	The Expression and Significance of VEGF, VEGFR-1 and VEGFR-2 in Condyloma Acuminatum	Knowledge, attitudes and acceptance are not discussed
Yan Y	The study on vitamin A acid cream associated with human interferon ointment in the treatment of flat warts	Knowledge, attitudes and acceptance are not discussed
Yang J	The relationship between KDR, TSP-1 and Cervical squamous cell carcinoma Angiogenesis	Knowledge, attitudes and acceptance are not discussed
Yang X	Feasibility of Ultrasound Therapy for HPV Infection of the Uterine Cervix	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Yang X	The expression of RUNX3 cervical cancer and its proliferation effect on Hela	Knowledge, attitudes and acceptance are not discussed
Yang HY	Experimental studies of pelvic endometriosis by Chinese medicine treatment	Knowledge, attitudes and acceptance are not discussed
Zhao P	DNA vaccine preparation of HLA specific HCMV Tandem epitopes of adenovirus and evaluation of immune effects	Knowledge, attitudes and acceptance are not discussed
Zhao FH et al	Research on a variety of cervical cancer screening programs	Knowledge, attitudes and acceptance are not discussed
Zhao XL	Study on association between DNMTI and DAPK and in vitro inhibition of DNMT1 expression	Knowledge, attitudes and acceptance are not discussed
Zhao FH	Cervical cancer screening methods and strategies	Knowledge, attitudes and acceptance are not discussed
Zhang JF et al	Research on HPV 16 Gastrointestinal gene vaccine	Knowledge, attitudes and acceptance are not discussed
Zhang W	The review of interferon in the treatment of cervical cancer and precancerous lesions	It's a general review
Zhang X	The prevalence of HPV infection and CIN in Shenyang city	Knowledge, attitudes and acceptance are not discussed
Zhang YB et al	High school biology knowledge links	Not a research report
Zhang JH et al	The detection of cervical cancer in high risk women	Knowledge, attitudes and acceptance are not discussed
Zhang JM et al	Diagnosis and differential diagnosis of Precancerous lesions of the uterine squamous cell carcinoma	Knowledge, attitudes and acceptance are not discussed
Zhang RZ et al	Research progress on the health education of cervical cancer patients	It's a general review
Zhang WJ et al	Clinical features and prognostic analysis of young women with cervical cancer	Knowledge, attitudes and acceptance are not discussed
Zhang X et al	HPV infection and Chinese medicine treatment on women in Shenyang city	Knowledge, attitudes and acceptance are not discussed
Zhang JL	Investigation research of the Uygur women cervical lesions and the HPV 16 infection in Xinjiang Ka Shi sharp Tao le townshiop	Knowledge, attitudes and acceptance are not discussed
Zhou YB et al	Research on HPV 16 L1 gene and Recombinant adenovirus vaccine	Knowledge, attitudes and acceptance are not discussed
Zhou N	Survey of Prevalence and Behavioral Risk Factors for AIDS/STD Among Female Sex Workers in Tianjin	Knowledge, attitudes and acceptance are not discussed
Zhang RZ et al	Health education progress of cervical cancer patients	It's a general review
Zhao DJ et al	The prevalence study on the HPV infection and the risk factors of the community female population in Shanghai	Knowledge, attitudes and acceptance are not discussed
Zheng GQ et al	The study on Artificial vaginoplasty by Sigmoid	Knowledge, attitudes and acceptance are not discussed
Zhou QZ et al	The correlation between genital tract HPV infection and cervical lesions among Shenzhen women.	Knowledge, attitudes and acceptance are not discussed
Zhu YS et al	An analysis of risk factors of cervical carcinoma and cervical intraepithelial neoplasia	Knowledge, attitudes and acceptance are not discussed
Zhan HY et al	The value for Cervical conization lesions residues after endocervical curettage surgery and HPV testing	Knowledge, attitudes and acceptance are not discussed

Study	Title	Exclusion reasons
Zhou KZ et al	The relationship between HPV infection and cervical lesions among women in Shenzhen	Knowledge, attitudes and acceptance are not discussed
Zhou WY et al	The nursing of cervical intraepithelial neoplasia with LEEP conization	Knowledge, attitudes and acceptance are not discussed
Zhao SP et al	Prevalence of cervical intraepithelial neoplasia and its risk factors among rural minority married women	Knowledge, attitudes and acceptance are not discussed
Zhang XL et al	Effect of psychological intervention on the life quality of patients with cervical human papillomavirus infection after treatment	Knowledge, attitudes and acceptance are not discussed
Zhang XL et al	The influence of psychological intervention on the quality of marital in the CIN Ⅰ patients with human papilloma virus	Knowledge, attitudes and acceptance are not discussed
Zhang GY et al	Rat orthotopic small bowel transplantation model established by Three casing vascular anastomosis	Knowledge, attitudes and acceptance are not discussed
Zhang GY et al	The clinical analysis of Vulvar intraepithelial neoplasia	Knowledge, attitudes and acceptance are not discussed
Zhang YM	Comparison of detection methods and clinical implications of pregnancy-related Cervical intraepithelial neoplasia	Knowledge, attitudes and acceptance are not discussed
Zhang WJ et al	Clinical features and prognostic analysis of young women with cervical cancer	Knowledge, attitudes and acceptance are not discussed
Zheng GH et al	thepathogen distribution of 16-20 year-old female reproductive tract infection	Knowledge, attitudes and acceptance are not discussed
Zhao DQ	HPV-related test illustration	Not a research report
Zhu YS et al	The analysis of cervical cancer and precancerous lesions related risk factors	Knowledge, attitudes and acceptance are not discussed
Zhou L et al	Analysis on prevalence status and high risk factors of female cervical diseases in Changchun	Knowledge, attitudes and acceptance are not discussed
Zhou XR et al	Quality analysis of cervical cytology diagnosis	Knowledge, attitudes and acceptance are not discussed
Zhou JY et al	Analysis of influencing factors on compliance with colposcopy in cervical cancer screening project in Daxing District, Beijing City	Knowledge, attitudes and acceptance are not discussed
Zhang JM et al	Precancerous lesions and differential diagnosis of cervical squamous cell carcinoma	Knowledge, attitudes and acceptance are not discussed
	Sexually transmitted diseases are not necessarily sexually transmitted	It’s not a research report
Zhang YL et al	The clinical analysis of prevalence of HPV infection in cervical cancer patients	Knowledge, attitudes and acceptance are not discussed
Zhang SH et al	CYP1A1 gene polymorphism and the relationship between HPV infection and Cervical squamous cell carcinoma	Knowledge, attitudes and acceptance are not discussed
Zhang WY et al	The relationship between high risk HPV and the severity of cervical cancer	Knowledge, attitudes and acceptance are not discussed
Zhang N	The study on Proliferation and apoptosis factors in Pseudo-condyloma and genital warts	Knowledge, attitudes and acceptance are not discussed
Zhang J	The study on HPV infection in cervical tissue and local immune state	Knowledge, attitudes and acceptance are not discussed
Zhang HP	The expression and implication of Livin and Smac in the genital warts tissue	Knowledge, attitudes and acceptance are not discussed
Zhang LJ et al	The clinical implication of high risk HPV detection in high degree of cervical intraepithelial neoplasia	Knowledge, attitudes and acceptance are not discussed

Appendix 3: Quality assessment of each individual study in my systematic review

The quality assessment of Chen J study (13 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (17-79), gender (women), and sample size (123 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected during two months in 2010 in one selected hospital and the HPV positive outpatients were selected to do the telephone interview. But the study didn't mention who conducted the telephone interview.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were HPV positive outpatients. There were no exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The sample was collected in one hospital from March to April in 2010, it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The participation rate was 100%. The study didn't report any inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the way through which health information delivered were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. χ^2 test was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess confounding like demographic, socio-economic, or other factors.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 100% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders such as ethnicity, occupation and so on.

The quality assessment of Cui B study (20 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (15-59), gender (women), and sample size (1160 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in seven selected hospital and the selected villages. The study use cluster sampling method to approach participants.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion is women aged between 15-59 years old who are able to behave normally.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method. The sample was collected from seven hospitals and selected villages, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate and inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, HPV vaccine, knowledge difference by education, and the targeted population were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2 test and spearman correlation were used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like educational level, urban/rural residence.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 96.7% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by educational level and urban/rural residence to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	Yes. The researcher mentioned ethnicity, occupation as potential bias.

The quality assessment of Fu FH study (14 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (40-95), gender (women), and sample size (2952participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected during twelve days in April in 2008 in three selected communities in Shijingshan district. The study was conducted by the trained researchers through face to face interview.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were women over age 40. There were no exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The sample was collected in three communities in April in 2008, it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate and inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the awareness difference among different age and education were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. χ^2 test was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as age, education level.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 98.4% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders such as ethnicity, occupation and so on.

The quality assessment of Fan XF study (11 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (28-60), gender (women), and sample size (242 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The study didn't mention by whom, when, where and how the sample was collected.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The exclusion criteria were women who conducted hysterectomy. The inclusion criteria were women aged 28-60 with low medical insurance.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. Little is known about how the sample was collected, so it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate and inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the risk factors of cervical cancer were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. t test was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study didn't assess confounding like demographic factors, socio-economic factors.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 97.6% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders such as ethnicity, occupation and so on.

The quality assessment of Fan BJ study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (19-72), gender (women), and sample size (962 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from January to December in 2008 in the outpatients department of Liaoning cancer hospital.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used random cluster sampling method. The sample was collected in one hospital in 2008, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate and inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, HPV vaccine, the willingness to be vaccinated were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. T test was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as education level.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 96.2% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by educational level to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders such as ethnicity, occupation and so on.

The quality assessment of Feng SW study (22 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (18-50), gender (women), and sample size (1432participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from March to August in 2010 in selected hospitals in Hangzhou and Lishui. The study was conducted by the trained researchers.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women who had normal communication ability. The exclusion criteria were age <18 or >50, ever had cervical disease, ever had psychiatric disease and so on.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, attitude toward HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	Yes. The study conducted test-retest reliability test, calculate Cronbach α when assessing the questionnaires. The Cronbach α was 0.87, the test-retest reliability was 0.63-0.93.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive, bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. T test, χ^2 test, linear regression was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	Yes. It conducted multivariate correlation analysis to analyse education, age and economic status was correlated with knowledge of HPV infection.
	12. Was modelling and multivariate techniques appropriate?	Yes. The multivariate correlation analysis was appropriate.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like urban/rural residence.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention how many enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by urban/rural residence to correct controllable variables. It also conducted multivariate analysis to adjust demographic factors.
	17. Did the researchers describe all potential bias or unmeasured confounders	Yes. The researcher mention other potential bias such as age, education and economic status and so on.

The quality assessment of Gao L et al study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (30-59), gender (women), and sample size (2648 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected during five months in 2008 in Linxiang District in Yunnan. The sample of rural women was collected by the researchers in CDC by using questionnaires.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were rural women who are volunteers to join in the study. There were no exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The sample was collected in one district during four months in 2008, so it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	Yes. The participants were all volunteers The study didn't report any inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the awareness difference among different ethnicity and education were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Latent classes analysis and latent class model was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	Yes. It conducted multivariate analysis, latent classes analysis.
	12. Was modelling and multivariate techniques appropriate?	Yes.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as ethnicity, education level.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't report the percentage of enrolled participants.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by ethnicity and education to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	Yes. The researcher mentioned other potential bias or unmeasured confounders such as ethnicity, education, age, marital status and so on.

The quality assessment of Guzhanuer A study (12 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described gender (men), and sample size (560 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected during three months in 2008 in Hetian District in Xinjiang. The sample of men was collected through their wives who joined in the cervical screening program.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were men who are husbands of women taking part in the cervical screening in the study. There were no exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The sample was collected in one district during three months in 2008, so it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The participants were all volunteers. The study didn't report any inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the awareness difference among different education were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	No. The study didn't mention any statistical analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as, education level.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't report the percentage of enrolled participants.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by education to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Gulinuer A study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-65), gender (women), and sample size (248 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected during four months in 2006 in Bozhou hospital in Xinjiang. The sample of women outpatients were collected by the doctors by using questionnaires.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were women outpatients. There were no exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The sample was collected in one hospital during four months in 2006, it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The participation rate was 100%. The study didn't report any inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the awareness difference among different occupation and education were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. χ^2 test was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as occupation, education level.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't report the percentage of enrolled participants.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by occupation and education to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Guzhalinuer A study (10 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (23-76), gender (women), and sample size (400 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in five selected hospitals in Xinjiang. The questionnaire was filled by the doctors.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were Uighur women. There were no exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The sample was collected in five selected hospitals, so it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The participation rate was 100%. The study didn't report any inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the risk factors of cervical cancer were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	No. The study didn't report which statistical test was conducted in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	No. The study didn't report the power calculation.
	14. Was there an assessment of confounding?	No. The study didn't assess confounding like demographic factors, socio-economic factors. .
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't report the percentage of enrolled participants.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders such as ethnicity, occupation and so on.

The quality assessment of Huang GF study (14 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-58), gender (women), and sample size (196 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The sample was collected in 2008. But the study didn't mention where, by whom and how the sample was collected.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged 20-58. The exclusion criteria were women who had hysterectomy, pelvic radiation therapy, who were in menstrual period and pregnancy.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method they used. The study didn't mention where and how the sample was collected, so it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. The willingness of women to be vaccinated were provided
	7. Was the measurement method valid?	N/A. The questions were not provided in the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive and bivariate statistical analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. χ^2 test was used in the data analysis.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct any multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as age.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't report the percentage of enrolled participants.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by using different age group to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of He M study (18 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (18-82), gender (women), and sample size (9865 women outpatients and 780 health professionals) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in 14 selected hospitals in seven regions of China from 2007 to 2009. The questionnaire was filled in by the participants.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study conducted multi-centre clinical survey to collect sample. The sample was collected in 14 selected hospitals, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the willingness to be vaccinated, the appropriate age for vaccination were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and multivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis, χ^2 test and logistic regression.
	11. Were multiple comparisons taken into consideration?	Yes. It conducted multivariate analysis, such as logistic regression.
	12. Was modelling and multivariate techniques appropriate?	Yes.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as age, education, income.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't report the percentage of enrolled participants.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted multivariate analysis to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	Yes. The researcher mentioned age, education, income and sex debut as potential bias.

The quality assessment of He X study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (16-26), gender (male and female), and sample size (1009 male and 1093 female students) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in two colleges. The questionnaire was filled in by the participants supervised by the trained researchers.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used stratified cluster sampling to collect sample. The sample was collected in two selected colleges, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the way through which they get the health information were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like demographic factors, such as gender.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 96.5% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by gender to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Jiang SY study (19 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-65), gender (women), and sample size (944 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one community of Hongkou district. The questionnaire was filled in by the participants supervised by the trained researchers.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged between 20 and 65. The exclusion criteria were women who never had sex experience, who had hysterectomy.
	4. Was the study population served as a probability sample?	Yes. The study used random cluster sampling to collect sample. The sample was collected in one community of Hongkou district, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like screening status, stratified by screening women and non-screening women.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 94.4% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by screening status to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Lu KN study (16 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (19-69), gender (women), and sample size (104 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from inpatients and outpatients in three Beijing hospitals from September to December in 2007.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There is no specific inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study used convenience sampling to collect sample. It wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness of HPV infection and knowledge of cervical cancer were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like educational status, stratified by high level education women and low level education women.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 94.5% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by education status to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Li J 2008 study (19 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (15-54), gender (women), and sample size (1013 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in Zhanlanlu community of Beijing city from June 2006 to June 2007. The interview-administrated questionnaire was conducted by the trained researchers.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged between 15 and 54. The exclusion criteria. were women who was in pregnancy, who had hysterectomy, who had pelvic radiation therapy and etc.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling to collect sample. The sample was collected in one community of Beijing city, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the willingness of being vaccinated were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding demographic factors like age, marriage, occupation, education.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	No. The study didn't mention what the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by age, marriage, occupation and education to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	Yes. The researcher mentioned age, marriage, occupation and education as all the potential bias.

The quality assessment of Li JM study (19 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (18-60), gender (women), and sample size (304 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one community of Baoan district of Shenzhen city. The questionnaire was filled in by the participants.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged between 18 and 65. The exclusion criteria. were women who had never sex experience, who had hysterectomy, and etc.
	4. Was the study population served as a probability sample?	Yes. The study used random cluster sampling to collect sample. The sample was collected in one community of Baoan district of Shenzhen city, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the risk factors of cervical cancer were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. χ^2 statistical test were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding like screening status.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	No. The study didn't mention what the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by screening status, like screening women and non-screening women.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Li XP study (11 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-50), gender (women), and sample size (300 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in Nanpu community of Wenzhou city. The questionnaire was filled in by the participants.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method. The sample was collected in one community of Wenzhou city, it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Li J 2011 study (16 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (36.5+9.6), gender (women and men), and sample size (160 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in Nanpu community of Wenzhou city. The questionnaire was filled in by the participants.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were health professionals in hospitals and rural clinic, government officials. There is not specific criteria to age and gender.
	4. Was the study population served as a probability sample?	Yes. The study used convenient, cluster and random sampling method. The sample was collected in one city of Dalian city and one county, it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, attitude and acceptability of HPV vaccines were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 90.9-94.1% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study stratified by education level to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Li CT et al study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-39), gender (women), and sample size (960 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The sample was collected in Tianshan community of Urumqi city. But it didn't mention from which setting the sample was specifically collected and when.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The study included women who had normal cognition, excluded women who had Hysterectomy history and pelvic radiation therapy.
	4. Was the study population served as a probability sample?	No. Cluster sampling method was used. But it didn't mention where the sample collected. It wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study stratified the participants by age.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by age to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Liu ZH et al study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (14-18), gender (boys and girls), and sample size (848 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one high school in Xiangtan city. Five classes were randomly selected from three grades in the high school.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used stratified cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study report the participation rate was 94.2%, which is a high rate.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection was provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	Yes. The Cronbach α was 0.86 and the test-retest reliability was0.81.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and variance analysis, multiple linear regression were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Variance analysis, multiple linear regression were used.
	11. Were multiple comparisons taken into consideration?	Yes. It conducted multiple linear regression.
	12. Was modelling and multivariate techniques appropriate?	Yes.
	13. Was the power calculation provided?	Yes. $p<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 94.2% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Long XE study (9 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (>18), gender (not speficify), and sample size (286 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The sample was collected in one college. There wasn't specific sampling frame for the study population
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	No. The study didn't report which kind of statistical test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	No. The power calculation wasn't provided.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 90.5 of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Ma D et al 2012study (16 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-54), gender (women and men), and sample size (198 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one hospital of Tangshan city in May 2011 including both doctors and nurses.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The study didn't mention any inclusion and exclusion criteira.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method. The sample was collected in one hospital of Tangshan city, it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and attitude of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	Yes. The study didn't calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and χ^2 test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding by stratifying the sample by doctors and nurses.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. The study showed 99% of the enrolled participants completed the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Ma D 2010 study (18 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (16-56), gender (women), and sample size (249 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one community and one hospital outpatient department of Beijing city. The questionnaire was filled in by the participants.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged 16-56. The exclusion criteria were women who had hysterectomy.
	4. Was the study population served as a probability sample?	No. The study used the convenience sampling method to collect data. The sample was collected in one community and one hospital of Beijing city, it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	Yes. The study calculated Cronbach α when assessing the questionnaires. The Cronbach α was 0.72.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. The study conducted descriptive analysis and t test.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed confounding by stratifying the sample by community women and women outpatients.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Ren CL et al study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (18-58), gender (women), and sample size (1005 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The sample was collected Malan district in Xinjiang. There wasn't specific sampling frame for the study population
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women with normal cognition, no pregnant, no hysterectomy or pelvic radiation therapy.
	4. Was the study population served as a probability sample?	No. The study mentioned where the sample was collected, but with no sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. χ^2 statistical test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	No. The study didn't mention what percentage of participants completed the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification by ethnicity to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Song D study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-54), gender (women), and sample size (957 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one county. 5-year is defined as one group including 125 women.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged 20-54, women having normal cognition, no pregnant, no hysterectomy or pelvic radiation therapy.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and attitude and acceptability of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate tests were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive test and x^2 test were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P \leqq 0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assess education level and cervical cancer history as confoundings.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 95.7 of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Sun J 2010 study (18 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (21-60), gender (women), and sample size (301 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in the outpatients department of one hospital in Dalian city from February to March.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women with normal cognition, had sexual behaviour.
	4. Was the study population served as a probability sample?	No. The study used convenient sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	Yes. The study conducted reliability test and calculate Cronbach α which is 0.843, and pearson correlation is 0.831 when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and linear regression was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. F statistical test, t test and pearson correlation was used.
	11. Were multiple comparisons taken into consideration?	Yes. It conducted multivariate analysis, multivariate linear regression.
	12. Was modelling and multivariate techniques appropriate?	Yes.
	13. Was the power calculation provided?	Yes. $P \leqq 0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 97.1 of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Shi YY study (19 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-60), gender (women), and sample size (1200 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in one hospital, one community, and two villages by using cluster sampling.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women residents who aged 20-60, had no cervix operation, not pregnancy, and had no pelvic radiation therapy.
	4. Was the study population served as a probability sample?	Yes. The study conducted cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Risk factors for cervical cancer was provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 test were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study identified age as the confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 95.7%of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study stratified by age to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Wang HQ study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-53), gender (women), and sample size (257 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from four hospitals. The participants were gynaecologists and obstetricians. The study didn't mention who collected the sample.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/ exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study conducted random sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 test were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study identified age and education level as the confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 85.7% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study stratified by education level correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention any other potential bias.

The quality assessment of Wen LZ study (11 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (22-48), gender (women), and sample size (400 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in the outpatient department of one hospital from Jan to June in 2009 by researchers.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/ exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and awareness of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical and bivariate analysis was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 test were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mentions what was the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Wang QL study (12 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-70), gender (women), and sample size (886 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected in three counties in north mountain areas in Sichuan province by researchers.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/ exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection was provided
	7. Was the measurement method valid?	Yes. The questions were provided for the study and fulfil the objective of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	No. The study didn't mention the power calculation.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mentions what was the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Wu Y study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (>15), gender (women), and sample size (489 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The study didn't mention the specific sampling frame.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/ exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used random sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided for the study and fulfil the objective of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed age, education level as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 97.8% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention any other potential bias.

The quality assessment of Wang XM et al study (18 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (>25), gender (women), and sample size (2269 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The urban women were collected from physical examination centre and rural women were collected from cervical screening program during July and September, 2010.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The exclusion criteria were women with history of hysterectomy and pelvic radiation therapy.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided for the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed socio-economic status as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what percentage of participants completed the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention any other potential bias.

The quality assessment of Xiamixinuer A study (14 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (23-85), gender (women), and sample size (245 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from inpatients department of five hospitals in Xinjiang province from Jan in 2004 to Jul in 2006.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The inclusion criteria were cervical cancer inpatients aged 23-85. There were no exclusion criteria
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and awareness of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	No. The study didn't mention the power calculation.
	14. Was there an assessment of confounding?	Yes. The study assessed educational level and occupation as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what was the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study conducted stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Xiao W study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (21-74), gender (women), and sample size (368 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from outpatients department in one hospital in Beijing from Jan to Apr in 2008.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/ exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection, the acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study .
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 were used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed health intervention as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 97.4% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study stratified by health intervention to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention any other potential bias.

The quality assessment of Xing YX et al study (14 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (18-63), gender (women), and sample size (200 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from Yushu district in Qinghai from June to August in 2009.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. The study didn't have specific inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and cervical cancer were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis and χ^2 test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed educational level as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what percentage of participants completed the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study used stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Xu CY study (16 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (25-54), gender (women), and sample size (6339 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from 137 communities of 12 districts in Beijing from Mar in 2007 to Sep in 2008.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women residents who aged 25-54, who had no cervical surgery, who had no pelvic radiation therapy, who had no pregnancy.
	4. Was the study population served as a probability sample?	Yes. The study used multi-stage cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Risk factor of cervical cancer was provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical was conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.01$ is statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 99.8% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Xu LN study (20 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (15-59), gender (women), and sample size (1666 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from two urban districts and one rural county from Jun to Nov in 2009.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women aged 15-59 with normal cognition.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness and knowledge of HPV infection and HPV vaccine, acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and multivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test, logistic regression analysis was used.
	11. Were multiple comparisons taken into consideration?	Yes. It conducted multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	Yes.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed urban/rural residence as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 96.5% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by urban/rural residence to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Xie Y study (16 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (30-59), gender (women), and sample size (2000 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from three counties in Chengdu in August of 2008.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women residents who aged 30-59, who had no cervical surgery, who had no pelvic radiation therapy, who had no pregnancy. .
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection was provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 99.4% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization or stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Ye JR study (16 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (20-60), gender (women), and sample size (1120 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from one hospital and two villages in Dalingshan County from Jan in 2010 to Jan in 2011.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria women, who aged 20-60 and lived in Dalingshan County more than three years, had no history of cervical surgery.
	4. Was the study population served as a probability sample?	Yes. The study the stage cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection was provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. The study showed 100% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Zhang LJ study (13 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (18-54), gender (women), and sample size (100 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from one hospital in Shenzhen from Dec in 2006 to Sep in 2007.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were HPV positive women, who aged 18-54. The exclusion criteria were women who have any mental disorders or cognitive impairment.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection was provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	No. The study didn't mention what was the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias or unmeasured confounders.

The quality assessment of Zhao DJ study (14 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (16-54), gender (women), and sample size (997 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from two communities in one district of Shanghai.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed age, education level and occupation as confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	N/A. The study didn't mention what was the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher mentioned age, education level and occupation as other potential bias.

The quality assessment of Zhou JY study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (30-59), gender (women), and sample size (2000 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The sample was collected from one district of Beijing. The study didn't mention when and who conducted the sampling process.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women residents who aged 30-59, who had no cervical surgery, who had no pelvic radiation therapy, who had no pregnancy.
	4. Was the study population served as a probability sample?	Yes. The study used multi-stage cluster sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Knowledge of HPV infection and risk factors for cervical cancer were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.01 was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 97.8% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher mentioned age, education level and occupation as other potential bias.

The quality assessment of Zhou LX study (15 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (16-55), gender (women), and sample size (752 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The sample was collected from one community and one outpatient department of one hospital. The study didn’t mention when and who conducted the sampling process.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. The inclusion criteria were women residents who aged 16-55, who had no cervical surgery, who had no pelvic radiation therapy, who had no pregnancy.
	4. Was the study population served as a probability sample?	Yes. The study used random sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn’t report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness and knowledge of HPV infection and HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn’t conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn’t conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn’t assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 96.4% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn’t conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher mentioned age, education level and occupation as other potential bias.

The quality assessment of Zhou Y 2010 study (12 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (17-21), gender (male and female), and sample size (207 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The sample was collected from one college; the students were the freshmen in 2009.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness and knowledge of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. $P<0.05$ was statistical significant.
	14. Was there an assessment of confounding?	No. The study didn't assess any confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. 97.6% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization, stratification or statistical adjustment to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher mentioned age, education level and occupation as other potential bias.

The quality assessment of Zhou Y et al 2012 study (17 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (17-25), gender (women and men), and sample size (2293 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	Yes. The participants were collected from four grades of Nanhua university during Mar 9th and 11th in 2009. The researcher went to the dormitory of the university to collect data.
	3. Were there specific inclusion/exclusion criteria for all groups?	Yes. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	Yes. The study used random sampling method, and it was a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness and knowledge of HPV infection were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed gender and education level as the confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	Yes. The study showed 96.3% of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	Yes. The study was stratified by gender and education level to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention other potential bias.

The quality assessment of Zhou Y 2011 study (10 scores)

	Questions	Reasons
Description	1. Was the study population well described (including sample size justification)?	Yes. The study well described the age (15-59), gender (women), and sample size (500 participants) of the study population.
Sampling	2. Was there specific sampling frame for the study population?	No. The study didn't mention when, where and who conducted the sampling process.
	3. Were there specific inclusion/exclusion criteria for all groups?	No. There were no inclusion/exclusion criteria.
	4. Was the study population served as a probability sample?	No. The study didn't mention the sampling method, and it wasn't a random sampling.
	5. Was there other selection bias (low participation rate, or all-volunteer sample, or inappropriate control)?	No. The study didn't report any low participation rate, inappropriate groups of participants, and etc.
Measurement	6. Was the primary/ secondary outcomes clearly defined?	Yes. Awareness and knowledge of HPV infection and acceptance of HPV vaccine were provided
	7. Was the measurement method valid?	Yes. The questions were provided and could represent and fulfil the objectives of the study.
	8. Was the measurement method reliable?	N/A. The study didn't conduct reliability test or calculate Cronbach α when assessing the questionnaires.
Data analysis	9. Did the researchers conduct statistical testing?	Yes. Descriptive statistical analysis and bivariate analysis were conducted in the study.
	10. Did the researchers report which statistical tests were used?	Yes. Descriptive analysis, χ^2test was used.
	11. Were multiple comparisons taken into consideration?	No. It didn't conduct multivariate analysis.
	12. Was modelling and multivariate techniques appropriate?	N/A.
	13. Was the power calculation provided?	Yes. P<0.05 was statistical significant.
	14. Was there an assessment of confounding?	Yes. The study assessed occupation and education level as the confounding.
Interpretation of results	15. Did at least 80% of enrolled participants complete the study	No. The study didn't mention what was the percentage of the enrolled participants complete the study.
	16. Did the researchers correct for controllable variables to limit bias appropriately	No. The study didn't conduct randomization or stratification to correct controllable variables.
	17. Did the researchers describe all potential bias or unmeasured confounders	No. The researcher didn't mention any other potential bias.

Appendix 4: Questionnaire-English language

Knowledge of and attitudes towards HPV vaccine among Chinese teenagers

Thank you for agreeing to complete this questionnaire. Remember that this questionnaire is COMPLETELY CONFIDENTIAL, so please say exactly what your views are.

All the questions can be answered by ticking a box. Please try to answer all questions. The questionnaire will be approximately 15-20 minutes to complete. Please do NOT turn to the next page until you finish completing page 1.

Have you ever heard of the Human Papillomavirus (HPV)? *(NOTE: HPV is NOT the same as HIV/AIDS)*

☐ Yes (please complete Section 1, below)

☐ No (please go to Section2,, on page 2)

Section 1: What known about HPV infection, cervical screening and HPV vaccines

Here are some statements about HPV and cervical cancer: do you think they are true or false? *(Please tick as the example given below)*

Statement	**True**	**False**	**Don't know**
About HPV infection			
HPV may cause genital warts (***example***)	√		
HPV may cause cervical cancer			
Most HPV infections can be cleared without treatment			
Sometimes, a HPV infection can last years without symptoms			
HPV infection can be sexually transmitted			
Condom use lowers the risk of HPV infection			
HPV is an uncommon sexually transmitted infection in China			
Poor personal hygiene can increase the risk of getting HPV infection			
Having multiple sexual partners increases the chance of getting cervical cancer			
Early age at first sexual intercourse can increase the risk of getting HPV infection			
About cervical screening			
Cervical cancer screening can effectively prevent cervical cancer			
The human papillomavirus test can identify women who are at increased risk of cervical cancer			
About HPV vaccination			
Regular cervical screening is not necessary after HPV vaccination			
HPV vaccination is 100% effective against cervical cancer			
The HPV vaccines are most useful for those who already have had sex			

Section 2: Attitudes and Beliefs about HPV infection and acceptability of the vaccine

Please read the information in the box and then answer the following questions. Please do NOT change your answers in Section 1!

- Human papillomavirus (HPV) is a common infection. It gets the name because it can cause papillomatosis in skin or mucosa, such as common warts or genital warts and has nothing to do with nipple or breast. People can get HPV infection by sexual activity or by skin-to-skin contact. Both men and women could be infected with HPV.
- HPV infection is very common among young men and women, but 70 percent of infections will be get rid of by their own immune system in 1 year. 5-10 percent of infected women are at risk of developing cervical cancer. Cervical cancer is a common female cancer - each year there are over 75,000 new cases in China.
- The risk factors for cervical cancer are multiple sexual partners, having sexual activity at early age, early pregnancy, multiple pregnancies, smoking, and long term use of oral contraceptives. The protective factors are cervical screening, vaccination, and condom use.
- HPV vaccines are available and help to improve the body's ability to fight HPV infections, and ultimately prevent some cervical cancers
- The best suitable people to receive the HPV vaccines are teenagers who are never been exposed to HPV infections
- prevent some cervical cancers and genital warts.

Part 1: Attitude towards HPV infection and cervical cancer *(Please answer the question 1 to 8, please tick one box only on each line)*

		Very unlikely	**Somewhat unlikely**	**Somewhat likely**	**Very likely**	**Unsure**
1	How likely is it you will get HPV infection in the future?					
2	How likely is it you will get cervical cancer in the future (female only)?					
	How much do you agree with the following statements?	**Strongly disagree**	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Unsure**
3	If I had an HPV infection, it would have a serious impact on my physical health					
4	If I had an HPV infection, it would be disruptive to my social life					
5	If I had an HPV infection, it would be disruptive to my sexual relationship(s)					
6	If I had cervical cancer, it would have a serious impact on my physical health (female only)					
7	If I had cervical cancer, it would be disruptive to my social life (female only)					
8	If I had cervical cancer, it would be disruptive to my sexual relationship(s) (female only)					

Part 2: Attitude towards HPV vaccination *(Please answer the question 9 to 24, please tick one box only on each line. Please think carefully before answering the following questions)*

		Very unlikely	**Somewhat unlikely**	**Somewhat likely**	**Very likely**	**Unsure**
9	How likely is it you would accept an offer of vaccination against HPV infection and cervical cancer if the vaccine was offered to you now					
	How much do you agree with the following statements	**Strongly disagree**	**Somewhat disagree**	**Somewhat agree**	**Strongly agree**	**Unsure**
10	If someone is vaccinated with HPV vaccine, this will help them avoid HPV infection					
11	If someone is vaccinated with HPV vaccine, this will help them avoid cervical cancer					
12	If I have a HPV vaccination, it is no longer necessary to be screened for cervical cancer (female only)					
13	If I have a HPV vaccination, it may be appropriate to have less frequent screening for cervical cancer (female only)					
14	Having an HPV vaccination may lead to people having more sexual partners as they think their risk of disease is reduced					
15	I am concerned that HPV vaccines have not been proved effective in prevention of HPV and cervical cancer					
16	I am concerned that HPV vaccines may have side effects such as fatigue or fever.					
17	I am concerned that HPV vaccines may have major side effects such as long term illness.					
18	I am worried that the HPV vaccine costs too much (CNY￥2000) and I don't want to pay such a high cost for the vaccine					
19	I trust the companies that make HPV vaccines					
20	I would get vaccinated if my friends recommend me to do so					
21	I would get vaccinated if my parents recommend me to do so					
22	I would get vaccinated if doctors or nurses recommend me to do so					
23	I would get vaccinated if there is a school requirement for me to be vaccinated					
24	I would get vaccinated if public service ads on TV or internet recommend it					

Part 3 Attitudes towards those with HPV infection

24. People will think that someone who is infected with HPV is a person who is promiscuous

Strongly disagree somewhat disagree somewhat agree strongly agree unsure

☐ ☐ ☐ ☐ ☐

25. If someone has HPV infection, people will gossip

Strongly disagree somewhat disagree somewhat agree strongly agree unsure

☐ ☐ ☐ ☐ ☐

26. People are infected because they or their partners have been unfaithful

Strongly disagree somewhat disagree somewhat agree strongly agree unsure

☐ ☐ ☐ ☐ ☐

27. One should keep a social distance from those who are infected with HPV

Strongly disagree somewhat disagree somewhat agree strongly agree unsure

☐ ☐ ☐ ☐ ☐

Section 3: Questions about you (Please remember all your answers are CONFIDENTIAL. We will not share your response with others)

1. **What is your gender?**

☐ Male ☐ Female

2. **What is your age?**

____

3. **Which school are you studying?**

☐ Mudanjiang No.1 high school ☐ Mudanjiang No. 2 high school

☐ Mudanjiang No.3 high school ☐ Ning'an high school

☐ Hailin high school

4. **Where do you live?**

☐ city ☐ countryside

5. **Which of the following best describes you?**

PLEASE TICK ONE BOX ONLY

I have never tried smoking ☐ I smoke some days ☐

I have only tried smoking once or twice ☐ I smoke every day ☐

I used to smoke but I have given up ☐

Thank you very much for taking part in the questionnaire survey and your answers are kept strictly CONFIDENTIAL!

Appendix 5: Questionnaire- Chinese language

关于中国青少年 HPV 疫苗的知识和态度的调查

感谢您填写这份问卷！您的答案是**严格保密**的，所以请尽可能**如实**的回答。问题都是以单选题的方式列出。请尽量回答所有问题。您将花费 10-15 分钟完成此次问卷调查。再次感谢您的配合！注：在您完成第一页之前**请勿翻到第二页作答。**

你听说过人乳头瘤病毒吗 (HPV)?（请勿将 HPV 与 HIV 混淆，HIV 是艾滋病毒）

☐ 听说过 （*请继续回答第一部分内容*）

☐ 没听说过 *(请直接回答问卷第二部分，在第二页)*

第一部分: 有关人乳头瘤病毒（HPV），宫颈癌筛查和人乳头瘤病毒（HPV）疫苗的知识

有关知识问题	对	错	不知道
关于人乳头瘤病毒（HPV）			
人乳头瘤病毒（HPV）可导致生殖器疣 (范例)	√		
人乳头瘤病毒（HPV）可导致宫颈癌			
大多数人乳头瘤病毒（HPV）感染，在没有治疗的情况下可自行消退			
有时，人乳头瘤病毒（HPV）可无症状持续数年			
人乳头瘤病毒（HPV）可通过性途径传播			
使用避孕套可降低感染人乳头瘤病毒（HPV）的风险			
人乳头瘤病毒（HPV）在中国是非常少见的性传播疾病			
不良的个人卫生习惯可增加感染人乳头瘤病毒（HPV）的风险			
拥有多个性伴侣将增加患宫颈癌的机会			
过早的开始性生活可增加感染人乳头瘤病毒（HPV）的风险			
关于宫颈癌筛查			
宫颈癌筛查可有效的预防宫颈癌发生			
人乳头瘤病毒（HPV）测试能够识别处于患宫颈癌危险性较高的妇女			
关于人乳头瘤病毒（HPV）疫苗			
接种人乳头瘤病毒（HPV）疫苗后没有必要接受常规宫颈癌筛查			
人乳头瘤病毒（HPV） 疫苗对预防宫颈癌 100% 有效			
人乳头瘤病毒（HPV）疫苗对已经有过性行为的人最有效			

第二部分: 对于人乳头瘤病毒（HPV）及其疫苗的态度和接受度

请仔细阅读以下关于人乳头瘤病毒（HPV）及其疫苗的内容，并回答随后的问题。阅读完请勿返回到第一部分修改答题内容，谢谢！

- 人乳头瘤病毒（HPV）是常见的病毒感染，其得名是由于 HPV 可导致皮肤或粘膜的乳头状瘤样增生，如寻常疣（俗称瘊子）和生殖器疣，与人的乳头或乳腺无关。HPV 可通过性，皮肤接触等途径传播。男性和女性都有可能无症状感染 HPV。
- HPV 感染在年轻的男性和女性中非常常见，但 70%感染者在 1 年内可通过自身免疫清除病毒。5-10%的 HPV 长期感染者将有可能患宫颈癌。宫颈癌是常见的女性肿瘤，每年中国有超过 75,000 新发病例。
- 感染 HPV 及患宫颈癌的**危险因素**有：过早性生活，多个性伴侣，早育，多产，吸烟，长期口服避孕药等。其**保护因素**有：接种疫苗，使用避孕套，进行宫颈癌筛查。
- HPV 疫苗已研制出来，可帮助机体对抗 HPV 感染，预防宫颈癌和生殖器疣。
- HPV 疫苗最适宜的接种对象是那些没有感染 HPV 的青少年。

1 关于 HPV 感染的态度

(请回答 1-8 单选题，每题选择一个最适合的答案)

	题目	非常不可能	不可能	可能	非常可能	不确定
1	与同龄人相比，你将来感染 HPV 的可能性有多大？					
2	与同龄人相比，你将来患宫颈癌的可能性有多大？（女生回答）					
	你是否同意以下说法	非常不同意	不同意	同意	非常同意	不确定
3	如果我感染了 HPV，它对我的健康危害很大					
4	如果我感染了 HPV，它将很大的影响我的社交生活					
5	如果我感染了 HPV，它将很大的影响我与性伴侣的关系					
6	如果我患宫颈癌，它对我的健康危害很大（女生回答）					
7	如果我患宫颈癌，它将很大的影响我的社交生活（女生回答）					
8	如果我患宫颈癌，它将很大的影响我与性伴侣的关系（女生回答）					

2 关于 HPV 疫苗的态度

(请回答 9-24 单选题， 每题选择一个最适合的答案，在您回答前请仔细思考)

	题目	非常不可能	不可能	可能	非常可能	不确定
9	如果现在有 HPV 疫苗预防人乳头瘤病毒（HPV）感染和宫颈癌，你打算接种 HPV 疫苗的可能性有多大					
	你是否同意以下说法	非常不同意	不同意	同意	非常同意	不确定
10	如果有人接种 HPV 疫苗，那可帮助他/她预防 HPV 感染					
11	如果有人接种 HPV 疫苗，那可帮助她预防宫颈癌					
12	如果我接种 HPV 疫苗，就没有必要进行宫颈癌筛查					
13	如果我接种 HPV 疫苗，有必要减少宫颈癌筛查的次数					
14	接种 HPV 疫苗会使人们拥有更多的性伴侣，因为大家认为患病（HPV 感染及宫颈癌）风险降低了					
15	我担心 HPV 疫苗在预防 HPV 感染和宫颈癌方面不是十分有效					
16	我担心 HPV 疫苗有轻微的副作用，如疲劳或发烧					
17	我担心 HPV 疫苗有严重的副作用，如长期患病					
18	HPV 疫苗太贵（约 2000 元人民币），我不想负担高额费用去接种疫苗					
19	我信任生产疫苗的公司					
20	如果我的朋友建议我接种疫苗，我会去接种					
21	如果我的父母建议我接种疫苗，我会去接种					
22	如果医生或护士建议我接种疫苗，我会去接种					
23	如果学校有要求接种此疫苗，我会去接种					
24	如果电视或者网络上的公益广告建议我接种疫苗，我会去接种					

3 对感染人乳头瘤病毒（HPV）的态度

26. 人们会认为 HPV 感染者是性行为不检点的人

非常不同意 ☐　不同意 ☐　同意 ☐　非常同意 ☐　不确定 ☐

27. 如果有人感染 HPV 病毒，别人会说闲话

非常不同意 ☐　不同意 ☐　同意 ☐　非常同意 ☐　不确定 ☐

28. 被感染 HPV 的人，是因为他自己或者性伴侣不忠诚

非常不同意 ☐　不同意 ☐　同意 ☐　非常同意 ☐　不确定 ☐

29. 最好对 HPV 感染者保持距离

非常不同意 ☐　不同意 ☐　同意 ☐　非常同意 ☐　不确定 ☐

第三部分: 关于你的问题

1. 你的性别是?

☐ 男性　☐ 女性

2. 你的年龄是? ____________

3. 你吸烟吗?

☐ 从来不吸　☐ 有时候吸烟

☐ 曾经吸过一两次　☐ 每天都吸烟

☐ 吸过烟但已戒掉

4. 你在哪所高中上学?

☐ 牡丹江市第一中学　☐ 牡丹江市第二中学

☐ 牡丹江市第三中学　☐ 宁安市高级中学

☐ 海林市高级中学

5. 你家住在农村还是城市?

☐农村

☐城市

感谢您参与此次调查！您的回答将是严格保密的！

Appendix 6: Ethical approval in China-Chinese language

牡丹江医学院医学伦理审查申请表

项目名称	中国青少年对于 HPV 疫苗的知识和态度调查		
项目负责人	David weller	职称	教授
电话	13810186592	电子信箱	D.Wang-8@sms.ed.ac.uk
所在单位	英国爱丁堡大学公共卫生学院		

单位伦理委员会意见：

经牡丹江医学院医学伦理委员会讨论，该项目研究涉及医学伦理方面工作符合《赫尔辛基宣言》及国际医学科学组织委员会颁布的《人体生物医学研究国际道德指南》中规定的道德准则，同意进行该项目研究。

伦理委员会成员签字：姚黎荣 张金凤
李国权 杨帆

伦理委员会主任签字：谷桂菊 单位伦理委员会公章：

2013 年 3 月 22 日

Appendix 7: Invitation letter-English Language

Invitation to take part in a questionnaire survey

Knowledge of and attitudes towards HPV vaccine among Chinese teenagers

You are being invited to take part in a research study that I'm carrying out as part of my PhD studies at the University of Edinburgh in the United Kingdom.

My project is looking at issues relating to the potential future introduction of the HPV vaccine among teenagers in China (HPV stands for Human Papillomavirus: it is linked to different types of cancers, and a vaccine has been developed to protect people from this virus).

I am in China from April to May 2013 to try to better understand the awareness and attitudes of teenagers like you in Heilongjiang province towards the HPV vaccine. I am asking you to complete a short questionnaire. Your responses will help influence decisions about the future introduction of the HPV vaccine in China.

Everyone's responses will be anonymous. You are asked to give answers to the questions in the questionnaire by yourself. No one will know what your responses are. We want to find out the honest views of people your age, even if you think you don't know much about HPV.

Your participation in this survey is voluntary and you may stop your participation at any time. The questionnaire will take about 15-20 minutes to fill out, and would be completed during a self-study course in your class. All information in the questionnaires will remain completely confidential.

Please read the information sheet for further information, and if you are willing to help please let me know.

Best wishes.

Du Wang

DU WANG, PhD Student
Centre for Population Health Sciences, University of Edinburgh
Edinburgh, EH8 9AG. United Kingdom.

Appendix 8: Invitation letter-Chinese language

问卷调查的邀请信
中国青少年关于 HPV 疫苗的知识和态度

您好！

我写信给您是想邀请您参加我们的一项研究，作为我英国爱丁堡大学博士课题的一部分。

这项研究是探讨为中国青少年引进 HPV 疫苗的可行性（HPV 是人乳头瘤病毒，目前已有疫苗可以用来预防这种病毒的感染）。

我们将于 2013 年 3 月到 5 月在黑龙江省的青少年中调查关于 HPV 疫苗的知识和态度。我们根据国内外参考文献设计了调查问卷，您的参与和回答将使我们更好的了解引进 HPV 疫苗的机会与挑战。

您的回答将是匿名的。没有人会知道您是如何作答的。即使您不了解 HPV，我们也想知道像您年龄的人对问题的回答。

您是自愿参加此项研究并可以随时终止调查。问卷调查需要 15-20 分钟，将在您班级的自习课进行，但您的名字不会出现在问卷里及以后的研究结果中。

请您继续阅读我们的信息卡。如果您想参与问卷调查，请在后面的知情同意书上签字并交回调查员，谢谢！

祝好并期待您的回复。

王都 Du Wang
英国爱丁堡大学公共卫生学院
在读博士

Appendix 9: Information sheet-English Language

Information sheet for questionnaire survey
Knowledge of and attitudes towards HPV vaccine among Chinese teenagers

You have been invited to take part in a research study. Before you decide whether or not to take part, please read this information sheet carefully as it explains the purpose of the study and what we'd be asking you to do if you agree to take part. You may talk to others about the study if you wish. Please ask the researcher Du Wang if there is anything that is not clear, or if you would like more information.

What is the purpose of the study?
Ms Du Wang is a PhD student at the Centre for Population Health Sciences at the University of Edinburgh. , is examining issues relating to the potential future introduction of the HPV vaccine among teenagers in China (the Human Papillomavirus vaccine can protect against many cases of cervical cancer). One part of the project is a questionnaire survey among teenagers in China to try to better understand the awareness and attitudes of teenagers towards the HPV vaccine: this questionnaire survey is being carried out in the spring of 2013. The questions are similar to those used in other surveys in China, and among teenagers in other countries. The results of the survey will give valuable information about introducing the HPV vaccine in China: help draft the materials to initiate health educational campaigns on HPV vaccines that best meets the information needs of young people in China.

Why have I been invited?
Adolescents aged from 15-18 years old in Mudanjiang city and Ning'an and Hailin County in Heilongjiang province are being asked to take part. You are a student at a high school in these three regions of Heilongjiang province where this study is being conducted and so you are invited to take part.

What will happen to me if I take part in?
The study will be conducted at your school by the researcher, Du Wang. Du Wang will explain in class why and how she will conduct the survey and what you are expected to do. You will be given an invitation letter with this information sheet. Please read these: if you want you can discuss them with your parents or family if you want to take part in the survey. Two or three days later Du Wang will visit your school again. In a self-study course, if you consent to participate, you will be given a questionnaire to complete (expected to take 15-20 minutes). The whole process will be kept completely anonymous. You'll be asked to put your completed questionnaire into a box so that nobody can see how you respond to the questions. Because the questionnaire is anonymous, your personal information will not be known by others. You are able to withdraw from the study at any time without giving a reason. Du Wang will stay in the classroom to ensure students are able to complete the questionnaire in silence.

The questions in the questionnaire comprise three sections:

- section 1, knowledge of HPV infection and vaccines (questions asked like “what are the risk factors of HPV infection?” and etc.)
- section 2, attitudes towards HPV infection and vaccines (questions asked like “how likely is it you will get HPV infection in the future?” etc.)
- section 3, background characteristics. (questions include age, gender, regional characteristic of schools and self-reported lifestyle)

Are any medicines or treatments involved in this study?
No, this is simply a questionnaire study where we will ask for your knowledge and attitude of HPV vaccination.

What are the possible risks of taking part in?
There are no risks to taking part. Your responses will be kept completely confidential, and will not be shared with other students or school staff. Nobody will know how you respond to any of the questions.

What are the possible benefits of taking part in?
There are no direct benefits to you in taking part. However, your answers will help health workers to better understand the awareness and attitudes of teenagers, and help shape health education and health promotion about the HPV vaccine for teenagers in China in the future.

Will my taking part in the study be kept confidential?
Yes. Your teacher and classmates will know if you take part in the survey, but all your responses in the questionnaire will be kept confidential. Because while you are completing the questionnaire, the researcher will stay in the classroom to ensure that participants will not look across other participants’ form or chat with other students around. Once you finish your questionnaire, you will put your completed questionnaire into a box so that the head teacher, your classmates and researcher will not know how you respond in the questionnaire.

What will happen if I don’t want to carry on with the study?
You are free to withdraw from the study at any time. If you do withdraw, we will use the information already collected up to that point only with your consent. If you do not consent, we will destroy the questionnaire received from you.

Who is carrying out this study?
This study is being undertaken as part of a PhD research project for Ms DU WANG at The University of Edinburgh’s Centre for Population Health Sciences (contact details below).

What should I do now?
If you decide that you would like to take part in this study, please fill in the consent form and return it to the researcher when she visits your class again.

I want to know more about the study before I decide
If you would like more information about the study, you can speak to Ms DU WANG who is responsible for the study. Mobile: 13810186592 or duwang84@gmail.com or D.Wang-8@sms.ed.ac.uk

WE WILL ADD THE CONTACT DETAILS OF A NOMINATED PERSON FROM MUDANJIANG MEDICAL UNIVERSITY

THANKS FOR READING THIS INFORMATION SHEET

Appendix 10: Information sheet-Chinese language

信息卡
中国青少年关于 HPV 疫苗的知识和态度

我们诚邀您参加此项调查研究。在您决定参加调查前，请仔细阅读此信息卡关于此项研究的问题，它阐明了本次调查的目的和我们即将问的问题。您也可以和其他人讨论此项研究。如果有不清楚的地方或您需要更多关于此研究的信息，可以询问调查员。

此项研究的目的是什么?
英国爱丁堡大学公共卫生学院博士生王都，在做一项关于为中国青少年引进 HPV 疫苗的调查（HPV 为人乳头瘤病毒，可预防宫颈癌）。其中一项研究是调查中国青少年关于 HPV 疫苗的知识和态度，此研究将在 2013 年春天开展。调查的结果将会为中国引进 HPV 疫苗提供宝贵信息。

为什么我要参加?
我们将选取年龄 15-18 岁，在牡丹江市，海林市和宁安市 5 所高中就读的青少年参加此项调查。您在这三个城市的高中学习，正是我们研究开展的调查地，符合我们研究的入选标准。

我参加后将会怎样?
王都将在你所在学校开展调查。她将在班上为您讲解为什么以及如何开展调查。我们将发放邀请信，知情同意书给您。您可以与您的父母或家人讨论此项调查。如果您同意，请在知情同意书上签上您的名字。王都将会在两三天后再次来到学校。我们将在一个自习课上收回知情同意书，之后您将会收到一份调查问卷（问卷将花费您 15-20 分钟填写）。整个过程将完全保密。调查完后，请您将调查问卷放入纸盒内，故没有人会了解您是如何回答的。因为调查问卷是匿名的，所以别人也不会知道您的个人信息。如果您不同意，您可以随时撤出此项研究。

此项研究涉及药品及治疗等吗?
没有。这只是一项关于 HPV 感染及 HPV 疫苗的知识和态度的简单调查。

参加此项研究有潜在的风险吗?
一点也没有。我们将会询问一些私人问题，但您的回答是严格保密的。没有人会知道您是如何回答的。

参加此项研究的好处是什么?
我们这项调查没有直接的益处。我们希望通过了解 HPV 的知识和态度，更好的了解影响 HPV 疫苗接种的影响因素，从而帮助我们更好的设计并实施学校的健康教育。

参加此项研究是保密的吗?
是的。尽管您签署了知情同意书，但我们不会在任何报告及发表的文章中使用您的个人信息。您的老师和同学将会知道您参与了此次调查，但您的回答将是严格保密的。您将会把调查问卷放入事先准备好的纸盒内，所以您老师和同学将不会知道您是如何作答的。调查员在最后的数据分析中也不会知道您的个人信息的。

如果我不参加，会怎样?
您可在任何时候退出此项研究。如果您撤出，我们将征求您的同意来决定是否使用搜集上来的数据。如果您不同意，我们将销毁问卷。

谁实施此项研究?
此项研究是爱丁堡大学公共卫生学院学生王都的一项博士课题。旨在了解 HPV 疫苗的接受度。资金支持来自爱丁堡大学研究生院。

我现在做什么?
如果您决定参加此项研究，请您填好附在后面的知情同意书，并交回调查员。

在我决定前我想了解更多相关内容
如果您想了解此项研究的更多内容，请您联系王都女士。手机：13810186592 or 邮箱：duwant84@gmail.com or D.Wang-8@sms.ed.ac.uk。

非常感谢您阅读此信息卡!