The progress report

Research project entitled: Research for Development of an Optimal Policy Strategy for Prevention and Control of Cervical Cancer in Thailand

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I. Introduction

Cervical cancer is the second most common cancer which accounts for 12% of all cancers in women worldwide [1]. The disease caused approximately 470,600 new cases and 233,400 deaths per year with 83% of these cases found in developing counties [1]. Unfortunately, there has been no effective treatment for curing advanced stage of cervical carcinoma. Thus, the early detection of the abnormal cell growth by performing regular cytological screening either papanicolaou (Pap) smear or direct visual inspection has been recommended in usual clinical practice [2]. Recently, there have been substantial evidence supporting that persistent infection of the cervix with high-risk types of human papillomavirus (HPV) leads to the development of cervical cancer [3]. Therefore, HPV DNA method has been introduced as a specific test for the viral infection causing cervical cancer. However, the sensitivity, specificity, cost, advantages and disadvantages of these methods are varied [4-6].

In addition, a vaccine that prevents infections known to cause cervical cancer is now available though there are still many critical issues related to the introduction of new and expensive vaccine that need to be considered; namely whether the introduction of the HPV vaccine would place increase burden on public health system and financing system, whether the vaccine presents 'a good value for money' for public support, how to ensure its reliable long-term financing, and what needed to be done for integration of other preventive approaches such as secondary screening.

In Thailand, based on health burden in terms of disability adjusted life years (DALYs) loss, cervical cancer was ranked at the 13^{th} or 15^{th} of the overall disease burden in Thai women aged 15-59 or $\geq$ 60 years, respectively [7]. Presently, for women aged $\geq$ 35 years, the costs of both Pap smear and direct visual inspection (visual inspection with acetic acid--VIA) are covered by the Universal Health Coverage plan. Nevertheless, the coverage of Pap smear is still limited and precancerous treatment is restrictedly provided in some hospitals [8]. Until now, there is no systematic evaluation of alternative interventions (i.e., VIA, HPV DNA testing, and HPV vaccine) to be used for substituting Pap smear in order to improve the performance of the cervical cancer prevention program in Thailand [1]. The systematic evaluation would help healthcare decision makers in Thailand to determine an optimal policy strategy using mixed available interventions that yield significant benefits by maximizing the coverage with more appropriate interventions to be provided to different groups of target population.

A primary objective of this study is to generate reliable and relevant information to guide health policy choices about prevention and control of cervical cancer in Thailand as well as other similar settings, especially in developing counties with limited financial and infrastructure. This study consists of four work packages that aim to;

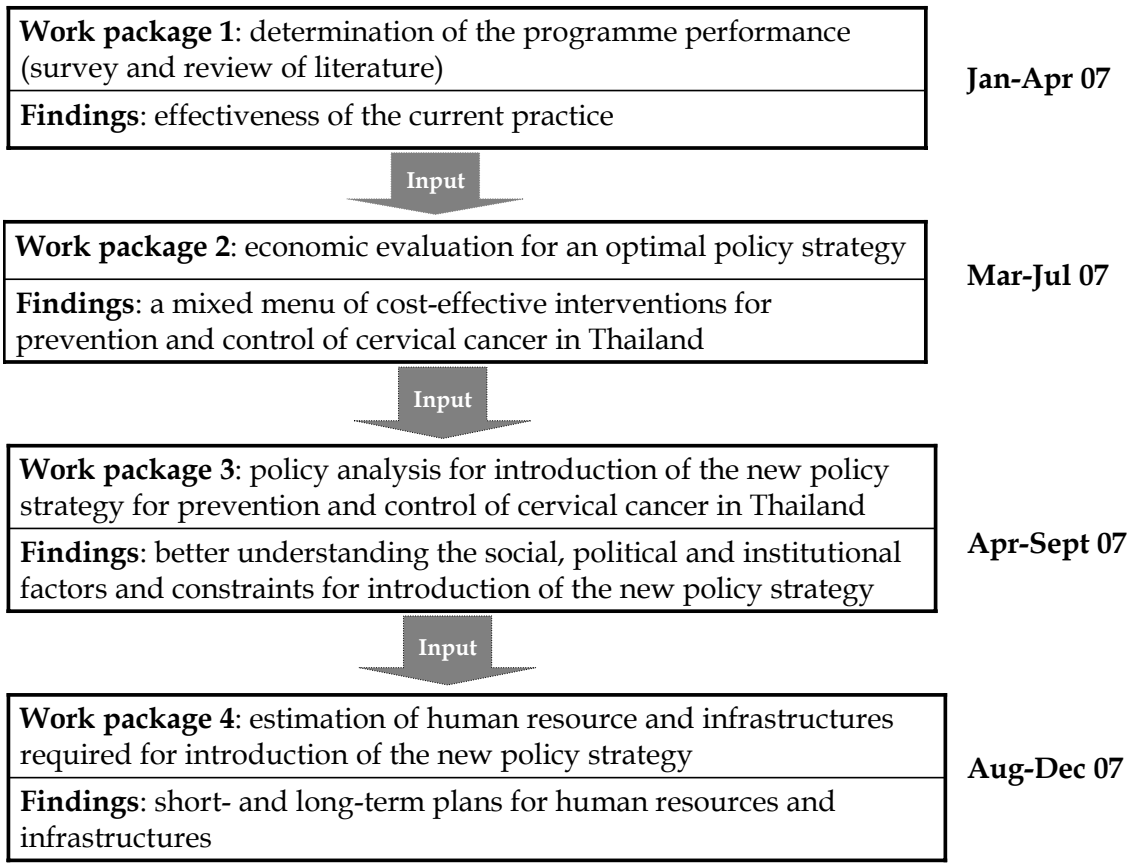
- assess the performance of the current cervical cancer prevention and control program carried out in Thailand;
- conduct health economic evaluation in order to achieve the optimum mix of interventions of screening (Pap, VIA and HPV DNA test) and HPV vaccines;
- understand the social, political and institutional factors and constraints for introducing the new policy strategy generated from economic appraisal;
- establish short- and long-term plans for human resources and infrastructure.

The study is carried out between January and December 2007 with the support from the Population and Reproductive Health Capacity Building Program of the World Bank.

II. Tasks performed and outputs produced

Based on the proposed timeline (Diagram 1), the first half of this year is to accomplish the work packages 1 and 2.

Diagram 1 overview of research methods used, expected outputs and timeframe



Due to unexpected difficulties in assessing survey data that caused the delay of work package 1 though the problems have already been solved and the work package 1 is nearly completed, a draft report of work package 1 is presented in an **appendix 1**. To sum up, an objective of the work package 1 is to determine the current situation of the coverage of cervical cancer screening programs among Thai females. The analysis focused on Pap smear and VIA screening, because Pap smear method has already been implemented at the national level for more than 20 years and a few years for VIA.

Data used for the analysis were obtained from the nationally representative household surveys. These include Health and Welfare Survey (HWS) and Reproductive Health Survey (RHS) conducted by National Statistical Office (NSO) in 2003 and 2006, respectively. Furthermore, the secondary data of screening activities for the VIA/SVA and Pap smear were retrieved from Cervical Precancerous Information System with Thai Modification (CPIStm) program and PapRegistry, respectively.

The performance was evaluated through the program outputs in terms of the screening coverage in the female population. Test results in the screened population were determined in terms of positive rate and completeness of the tests. In addition, human and physical resources available for the services were identified and compared with the service load. The qualitative method using an in-depth interview was used to explain the possible reasons behind practice variation found in the quantitative information.

The results are divided into six parts: (1) overall screening coverage, (2) variation by women ages, (3) variation by geographic regions of health care facilities, (4) trends in VIA and Pap smear coverage for provinces implementing both VIA and Pap smear, (5) variation by health care facilities, and (6) screening results. However, the results of in-depth interviews with health care providers and health managers at both district and provincial levels will be presented in the final report.

Based on the data from national health survey, the life-time screening coverage reported by RHS in 2006 increased to 63.3% in total. Even though the annual VIA coverage was not higher than the Pap smear coverage, the performance of VIA seemed to be better than Pap smear. Approximately 15-20% of the women receiving the cervical cancer screening were not in the national target ages[1]. This non-target fraction is similar between Pap smear and VIA. There was variation in the population coverage across geographic regions of the health care facilities that provided the cervical cancer screening services. The provinces that performed quite well on the VIA coverage also showed the above average performance on Pap smear screening. Pap smear was performed mostly at the sub-district health centers (66.0%). About 17.0% of the service recorded for Pap smear was not found the report on the quality of the slide preparation from the initial health care providers. Approximately 12% could not perform VIA because the squamus-columnar junction was not completely visible.

For the work package 2, using information from the work package 1 we are conducting an economic analysis on policy options for prevention and control of cervical cancer and this progress report includes results from three sub-studies of this work package that conducted literature reviews and, where applicable, meta-analyses for detection of (1) the methodologies that have been used in study of economic evaluation of prevention and control of cervical cancer, focusing on characteristics of decision analytic model (see detail in **appendix 2**), (2) the efficacy of HPV vaccine (see detail in **appendix 3**), and (3) the operating characteristics (sensitivity, specificity, positive predictive value and negative predictive value) of screening tests including VIA, Pap smear, and HPV DNA testing (see detail in **appendix 4**).

[1] Under an agreement between National Health Security Office (NHSO) and Ministry of Public Health (MOPH), both Pap smear and VIA are covered in the benefit package of NHSO. The screening frequency for each individual woman is set at every five years. The Pap smear target covers women at the 5-year interval between ages 35 and 60 years (i.e., 35, 40, 45, 50, 55, and 60 years). The target for VIA includes women younger than 45 years old and the VIA target ages are set at the range between 30 and 44 years by excluding 35 and 40 years which are the Pap smear target ages.

III. Description of tasks to be performed in the next six-month period

We plan to complete the work package 2 by September 2007 and the findings from the work package 2, a mixed-menu of cost-effective interventions for prevention and control of cervical cancer in Thailand, will be a significant input for conducting qualitative policy analysis of the work package 3. Finally, the estimation of human resource and infrastructures required for introduction of the new policy strategy will be estimated.

Appendix 1

Work package 1: the determination of the performance of the current programs for prevention and control of cervical cancer in Thailand

Introduction

Amidst an emergence of the promising primary prevention of cervical cancer through the use of human papillomavirus (HPV) vaccines, the secondary prevention through the pre-cancer screening is deemed an indispensable component. An efficacy of the screening strategies existing in developed countries has been understood. However, knowledge on the performance of screening programs in developing countries has rarely been up to date.

In Thailand, the conventional cytology known as Pap smear has been available for more than 40 years. This technique was used mainly for diagnostic purposes rather than for screening the cervical cancer. The national program of Pap smear screening is planned and supervised by the Department of Medical Services (DMS), Ministry of Public Health (MOPH). The National Cancer Institute (NCI) under DMS is responsible for maintaining the cervical cancer and other cancer registries. For monitoring and evaluation of the national implementation of cervical cancer screening, NCI just recently developed a large database of Pap smear services, called PapRegistry.

For the secondary prevention to have a major impact on the incidence of cancer, the coverage of screening programs in the population at risk should be as large as possible. The incidence of cervical cancer is expected to reduce by 55% if the effective screening coverage is at least 80% of the target population [8]. Besides, the women identified as having precancerous lesions need to have the lesions treated before they progress to an invasive cancer. The screen-and-treat coverage is claimed to be more important for reducing the cervical cancer incidence than the screening frequency alone (IARC, 1986). In such case, the effectiveness of the long-standing screening strategy like Pap smear that requires a tandem of health services has to be examined in terms of the continuum of care.

In the past, NCI reported that in several provinces the opportunistic Pap smear covered only 5% of the female population [8].Even as recently as 2005, the MOPH Division of Reproductive Health revealed that 37.7% of the women in reproductive ages (15-44 years) underwent the cervical cancer screening. It indicated that the existing national screening program could not effectively control or reduce the cervical cancer incidence.

In 2001, the Johns Hopkins Program for International Education in Gynecology and Obstetrics (JHPIEGO) Corporation in collaboration with the Royal Thai College of Obstetricians and Gynaecologists (RTCOG) introduced a direct visual inspection with acetic acid (VIA) as a cervical cancer screening alternative. An initial project launched in four districts of Roi-Et province in the northeast has demonstrated that the use of VIA followed by a cryotherapy (if tested positive) known as the single visit approach (SVA) was safe, acceptable and feasible [8]. During 2002-2004, only four

provinces (Roi-Et, Nong Khai, Yasothon, and Nakhon Phnom[2]) in the northeast region adopted the VIA/SVA program. In 2005, the program expanded to four provinces in the north and two provinces in the south. In 2006, this VIA/SVA program existed in a total of 17 out of 75 provinces, mostly at the district health system (DHS) level in the rural areas (a total of 186 districts).

For the nation-wide planning and implementation of the VIA program, the MOPH Department of Health (DOH) by Division of Reproductive Health assumes the role of national manager. The JHPIEGO Corporation Cervical Cancer Prevention Group helps organizing the 2-week competency-based VIA/SVA training module for registered nurses who will engage in this screen-and-treat service.

Beginning in 2005, National Health Security Office (NHSO) as the national manager of the universal health care coverage (UC) scheme boosted the cervical cancer screening program by establishing a service contract with MOPH who takes care of most health facilities in public sector, especially in the provincial areas. Based on such an agreement, NHSO would pay an individual health care provider who performs the screening activities to women at the target ages.[3]

Under this NHSO-MOPH agreement, both Pap smear and VIA are covered in the benefit package of NHSO. The screening frequency for each individual woman is set at every five years. The Pap smear target covers women at the 5-year interval between ages 35 and 60 years (i.e., 35, 40, 45, 50, 55, and 60 years) for each year of planning and implementation. The target for VIA includes women younger than 45 years old since the squamo-columnar junction (SCJ) of the cervix may not be seen completely in the older women. For ease of administration in the provinces that adopt both screening methods, the VIA target ages are set at the range between 30 and 44 years by excluding 35 and 40 years which are the Pap smear target ages. This nation-wide NHSO financial incentive and the VIA/SVA program in selected provinces are the two major recent developments expected to raise the performance of the national cervical cancer prevention and control program which is the focus of work package 1 (WP1) in this study.

Objective

This WP1 presents the results from an analysis of the current situation of the national cervical cancer prevention and control program in Thailand by examining the program performance of Pap smear and VIA with respect to certain important characteristics.

The performance was evaluated through the program outputs in terms of the screening coverage in the female population. Test results in the screened population were determined in terms of positive rate and completeness of the tests. In addition, human and physical resources available for the services were identified and compared with the service load. The qualitative method using an in-depth interview was used to

[2] Implemented in 2003 as a pilot in one district but later in 2006 the district quitted from the program.
[3] In 2005, the NHSO target for Pap smear was 0.6 million female in all 75 provinces, whereas the VIA target covered 0.1 million female in every district of 9 provinces (Roi-Et, Nong Khai, Yasothon, Amnat Charoen, Chiang Mai, Utraradit, Nan, Surat Thani, and Nakorn Srithamaraj) and one district in Phitsanulok.

explain the possible reasons behind practice variation found in the quantitative information.

Methodology

The population coverage of cervical cancer screening was estimated using two major sources of data. The first data set was obtained from the nationally representative household surveys. These include Health and Welfare Survey (HWS) and Reproductive Health Survey (RHS) conducted by National Statistical Office (NSO) in 2003 and 2006, respectively. Both surveys used the face-to-face structured interview based on event recalls. The HWS questionnaire asked a woman aged at least 35 years if she has ever had a cervical cancer screening in the past. The RHS focused on the female respondent aged 35-59 years and used a similar question. However, the RHS question clearly defined the screening frequencies and periods using the 5-year timeframe.

The second type of data is the electronic records of screening activities performed by health care personnel. The service encounter-level data were reported by health care facilities in two different formats. The first was for the VIA/SVA program which was initiated in 2000 by the JHPIEGO's SAFE project. This database is called Cervical Precancerous Information System with Thai Modification (CPIStm). The second database is PapRegistry. As mentioned previously, PapRegistry was developed by NCI in various versions for supporting the reporting and reimbursement system according to the NHSO-MOPH agreement since 2005.

The CPIStm database contains variables indicating the 13-digit personal identification number and age of the VIA recipient, screening date and health facility providing the service, and the screening result (positive vs. negative). In addition, the following cryotherapy and referral (if any) are recorded for the positive cases. Those who were not able to receive VIA (for example old ages or incomplete SCJ) and underwent Pap smear instead are allowed to be recorded in CPIStm. The CPIStm database covers the period of calendar years 2002 to 2006. Data are completed until December 2006. The records of Pap smear obtained from the CPIStm database were not used for further analysis.

The PapRegistry database covers similar information with regard to the Pap smear recipient, dates of slide fixation and slide reading, and service provider. The screening results including (un)matching slides, quality of the slide preparation (satisfactory vs. unsatisfactory), and epithelial (ab)normality result are recorded. The Pap smear data from PapRegistry have not been readily available until 2005. As of June 30, 2007, the PapRegistry data for the most recent year (2006) are still incomplete. The NCI has not finished matching the health facility records (i.e., from screeners) with the laboratory records (i.e., from slide readers).

Note: the analysis results on Pap smear coverage based on the PapRegistry database will be updated in the final report when the complete dataset is obtained from NCI through NHSO.

For a calculation of the population screening coverage, the denominator is generated from the total number of female population in various age categories specific to the

nationally set target under the NHSO-MOPH contract. This was obtained from the official population registration system which is maintained by the Ministry of Interior Department of Provincial Administration (DOPA). The population coverage was determined on an annual basis. The overall coverage was stratified by years of the service encounters, women's ages, and regional location of health care facilities that provided the screening services.

In addition, distribution of the screened women in each year was analyzed according to women's ages (by number of cases) and health facility types (by number of visits). One major point in estimating the population coverage needs to be distinguished between Pap smear and VIA due to the nature of target population. As Pap smear focuses on women whose ages are between 35-60 years and devisable by 5, its target population will move to the six totally new cohorts: 35, 40, 45, 50, 55, and 60 years for every rolling year. Hence, the effective coverage could be determined for each year independently based upon the new number of moving targets. In other words, the overall coverage during 2005-2006 could be estimated as the ratio of a summation of the screened cases by a summation of the total number of target women across two years.

For VIA, the target ages cover 13 categories in three separate ranges: 30-34, 36-39, and 41-44 years which exclude two categories (35 and 40 years) that are eligible to Pap smear screening. For the next year to come, only one new cohort that will turn to 30 years of age will become the target population, whereas those are already 44 years old will be no longer eligible for VIA. To allow for a repeated eligibility to VIA over five years in an individual woman, an annual population cannot be added up to become the denominator for an estimation of the overall coverage over the five-year period. Besides, only the province that has implemented the VIA program for the full 5 years (i.e., Roi-Et) could be determined if the final coverage met the goal or not.[4] In other provinces with less than 5 years of the VIA implementation, the cumulative screened cases divided by the average number of annual population should be perceived as the scaling up rather than the final coverage.

In-depth interviews were carried out with health care providers and health managers at both district and provincial levels. Three selected study provinces include Chiang Mai, Nakhon Phnom and Roi-Et. Key informants are health workers in the sub-district health centers, registered nurses in the district hospitals, gynecologists, laboratory technicians and cytologists in the provincial hospitals, heads of district health offices, and heads and staff of the provincial health office (PHO)'s Non-Communicable Disease (NCD) Departments. The interviewing guide covers issues around an identification of the target population, information, education and counseling on the cancer and prevention strategies, screening and referral procedures, and barrier to the screening program.

Results

1. Overall screening coverage

[4] Most provinces set the goal of VIA coverage as 80% within 5 years, whereas the goad for Pap smear is usually 50% annually. In this case, the final coverage for VIA should be estimated as the ratio between the cumulative annual cases and the 5-year average of target population.

1.1 National household surveys

1.1.1 Coverage in 2003

Based on the response to HWS in 2003, a total of approximately 4 million women aged at least 35 years in Thailand have received the cervical cancer screening at least once in the past (Table 1). This is correspondent to the life-time coverage of 37.7% of the population at risk to cervical cancer.

Table 1 Number of female population having cervical cancer screening in the past by place of living, 2003

	Inside municipality		Outside municipality	
	Not screened	**Screened**	**Not screened**	**Screened**
Bangkok	780,907	603,911	-	-
	(56.4%)	(43.6%)	-	-
Central	568,949	259,438	1,103,290	524,355
	(68.7%)	(31.3%)	(67.8%)	(32.2%)
North	240,103	217,908	1,016,924	695,035
	(52.4%)	(47.6%)	(59.4%)	(40.6%)
Northeast	342,179	241,816	1,932,166	1,040,228
	(58.6%)	(41.4%)	(65.0%)	(35.0%)
South	145,326	106,729	569,363	359,167
	(57.7%)	(42.3%)	(61.3%)	(38.7%)
Total	2,077,464	1,429,802	4,621,743	2,618,785
	(59.2%)	(40.8%)	(63.8%)	(36.2%)

Source: HWS 2003

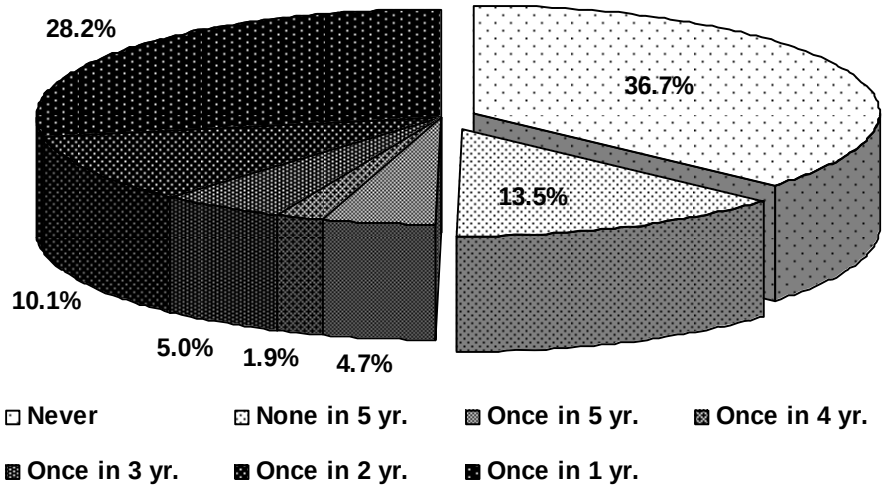
When broken down by the residence locations, women living inside the municipality area (except for the central region) exposed to the screening services more than the non-municipal counterparts. As much as 63.8% of those living outside the municipal area have never had their uterine cervix screened for the cancer. This probably reflects an issue of physical inaccessibility to health care facilities. However, a relatively lower rate of the screening in the central region (31.9%) as compared with other regional locations (42.1% in the north, 39.5% in the south, and 36.0% in the northeast) signals other factors that can explain variations in the utilization of cervical cancer screening services. Since HWS did not specify the exact time period and frequency of the screening each respondent received, the 37.7% coverage did not reveal magnitude of the screening guideline adherence and the true performance of the national cervical cancer prevention and control program.

1.1.2 Coverage in 2006

The most recent RHS provides a clearer picture on the effective coverage of cervical cancer screening in the Thai female population since the 5-year time frame was used as a reference for the recall. The life-time screening coverage reported by RHS in 2006 increased to 63.3% in total. Whether this is the effect from the NHSO initiative on financial incentive to the screening service providers first introduced in 2005 is unclear.

Of the 11.4 million estimated for the total number of women aged 35-59 years, 49.8% have been screened for cervical cancer at least once within the last 5 years, 13.5% have the screening beyond the 5-year period, and 36.7% have never been exposed to the screening services (Figure 1).

Figure 1 Fractions of women 35-59 years having cervical cancer screening in different intervals



Source: RHS 2006

The 2006 RHS shows quite a different pattern of the urban-rural variation in the cervical cancer screening from the HWS 2003. There was not much disparity in the 5-year screening coverage with respect to municipality, except for the southern region whereby the municipality area had screening fraction (49.7%) more than the non-municipality area (40.3%) (Table 2).

Table 2 Number of female population having cervical cancer screening in the past 5 years by place of living, 2006

	Inside municipality			Outside municipality		
	Never screened	Screened beyond 5 yr	Screened within 5 yr	Never screened	Screened beyond 5 yr	Screened within 5 yr
Bangkok	626,518	243,504	473,974	-	-	-
	(46.6%)	(18.1%)	(35.3%)	-	-	-
Central	345,472	148,853	401,894	749,159	293,791	816,667
	(38.6%)	(16.6%)	(44.8%)	(40.3%)	(15.8%)	(43.9%)
North	128,680	44,530	276,899	541,027	146,145	1,100,318
	(28.6%)	(9.9%)	(61.5%)	(30.3%)	(8.2%)	(61.6%)
Northeast	178,184	73,360	315,017	1,041,862	382,063	1,719,959
	(31.5%)	(13.0%)	(55.6%)	(33.1%)	(12.2%)	(54.7%)
South	116,837	47,596	162,172	454,681	163,896	417,761
	(35.8%)	(14.6%)	(49.7%)	(43.9%)	(15.8%)	(40.3%)
Total	1,395,691	557,843	1,629,956	2,786,729	985,895	4,054,705
	(39.0%)	(15.6%)	(45.5%)	(35.6%)	(12.6%)	(51.8%)

Source: RHS 2006

The highest coverage of 5-year screening was found in the northern region (61.5%). This 2006 RHS finding is congruent with that from HWS in 2003. Ironically, the lowest coverage (35.3%) was found in Bangkok, followed by the southern (42.6%) and central (44.2%) regions.

Women in the younger ages received the cervical cancer screening in a greater proportion than the older counterparts. The 5-year screening coverage is 51.4%, 53.1%, and 50.7% for the 35-39, 40-44, and 45-49 years of age; and 46.8% and 40.2% of the 50-54, and 55-59 year age groups, respectively. This age-reversing trend in the screening coverage was consistent in all geographic regions. The women aged 55-59 years living in the southern and the central regions were the lowest screened population (67.1% and 63.6%, respectively have not been screened within the last 5 years).

1.2 Facility-based records for national program

1.2.1 PapRegistry and CPIStm reporting systems

As mentioned previously, the two major sources of cervical cancer screening data at the national level are PapRegistry (for Pap smear) and CPIStm (for all VIA and some Pap smear). Reporting systems for Pap smear and VIA are different in several aspects. PapRegistry has a relatively short history of its evolvement as compared with CPIStm. The PapRegistry software was first developed in 2005 by NCI who is the national manager of Pap smear screening program under the MOPH DMS. The main purpose of PapRegistry development is to support the reimbursement system nation-wide under the NHSO-MOPH contract on incentive payment for the providers of Pap smear services which include slide fixing and reading. The PapRegistry software has been modified for two times since its inception.

The CPIStm software has been developed with the purpose to support the monitoring and evaluation of VIA/SVA which the MOPH DOH by Division of Reproductive Health is a national manager. The CPIStm system was initially implemented in 2000 under the JHPIEGO project in Roi-Et province. In 2006, the VIA/SVA program was expanded to 17 provinces which cover 186 districts in total (Table 3). The CPIStm software has been revised several times.

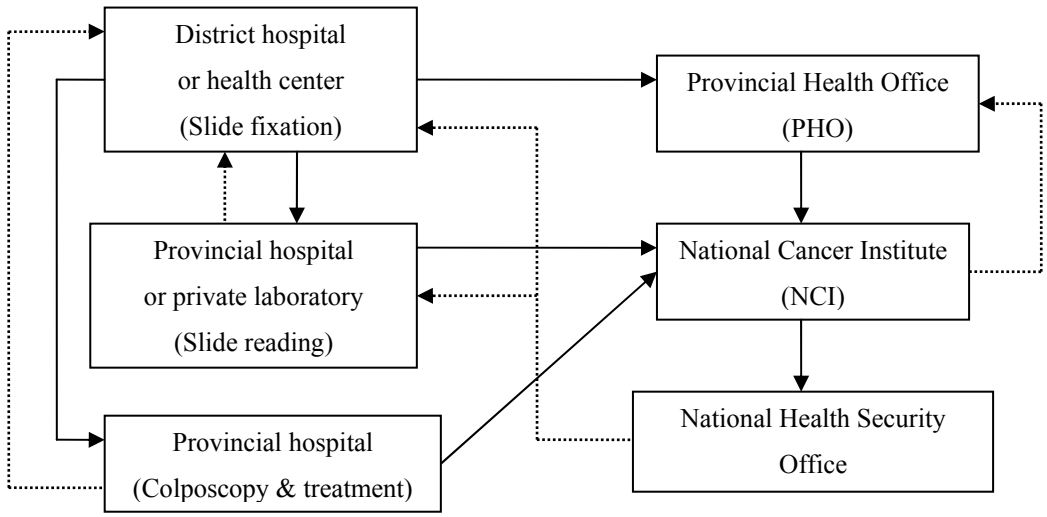
Table 3 Number of provinces and their districts adopting VIA program

	2002	2003	2004	2005	2006
Central	--	--	--	--	1 province[g] (11 districts)
North	--	--	--	4 provinces[d] (49 districts)	6 provinces[h] (69 districts)
Northeast	1 province[a] (20 districts)	3 provinces[b] (38 districts)	4 provinces[c] (47 districts)	5 provinces[e] (54 districts)	7 provinces[i] (56 districts)
South	--	--	--	2 provinces[f] (42 districts)	3 provinces[j] (50 districts)
Total	1 province (20 districts)	3 provinces (38 districts)	4 provinces (47 districts)	11 provinces (145 districts)	17 provinces (186 districts)

[a] Roi-Et
[b] Roi-Et, Nong Khai, and Nakhon Phnom (one district)
[c] Roi-Et, Nong Khai, Nakhon Phnom (one district), and Yasothon
[d] Chiang Mai, Utraradit, Nan, and Phitsanulok (one district)
[e] Roi-Et, Nong Khai, Nakhon Phnom (one district), Yasothon, and Amnat Charoen
[f] Surat Thani and Nakorn Srithamaraj
[g] Lopburi
[h] Chiang Mai, Utraradit, Nan, Phitsanulok (one district), Petchaboon, and Tak
[i] Roi-Et, Nong Khai, Yasothon, Amnat Charoen; and Srisaket, Ubon Ratchathani, and Mukdaharn (one district each)
[j] Surat Thani, Nakorn Srithamaraj, and Krabi

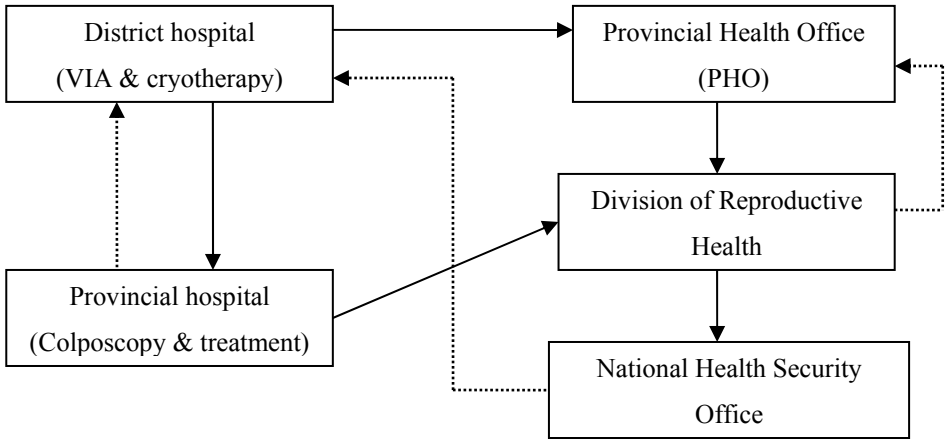
The PapRegistry data flow for Pap smear reporting system can be elaborated as follow (Figure 2). First, the service encounter-level data recorded by each health facility at DHS level (i.e., district hospital, sub-district health center) are sent to the cytology units of the provincial hospital or private laboratory offices for reading and interpretation of the fixed slides. This process can take weeks or months depending on the service workloads and laboratory availability. In each province, data from the cyto-screeners are pooled at the PHO NCD Department. The data are then forwarded to NCI for further verification by matching the slide fixing part with the slide reading part from the laboratory units which are also recorded in PapRegistry. If both parts are matched perfectly, the NCI-verified data will be transferred to NHSO for further reimbursement to health care providers.

Figure 2 Flow of Pap smear reporting system



For CPIStm, all VIA screening and cryotherapy records are transferred to the DOH Division of Reproductive Health through PHO (Figure 3). Since the screening and treatment is combined into a single visit, there is no need to wait for the confirmed result from laboratory unit. Only the suspicious cancer cases are referred to colposcopy at the provincial hospital for confirmed diagnosis and proper treatment.

Figure 3 Flow of VIA reporting system



As of June 2007, the PapRegistry and CPIStm databases contain the records on Pap smear and/or VIA screenings of 472,966 and 307,442 service encounters (or number of visits) in total, respectively (Table 4). The Pap smear data in PapRegistry are available only for 2005 and 2006 (Note: 2006 data are incomplete), whereas CPIStm covers the VIA (and Pap smear in certain cases) data from 2002 to 2006.

Table 4 Number of screening encounters by years of service and regions of health facilities as reported in PapRegistry and CPIStm

	PapRegistry (N = 472,966)	**CPIStm** (N = 307,442)[a]
Year		
- 2002	17	14,788
- 2003	39	45,397
- 2004	324	62,075
- 2005	234,866	107,392
- 2006	187,681	68,670
- Unknown	50,039	9,120
Region		
- Central	76,850 (18.0%)	535 (0.2%)
- North	110,928 (26.0%)	60,645 (19.7%)
- Northeast	191,970 (45.0%)	202,972 (66.0%)
- South	47,206 (11.1%)	43,233 (14.1%)
- Unknown	45,740	57

[a] Most are VIA visits though some include Pap smear for those not eligible to VIA at the service encounter

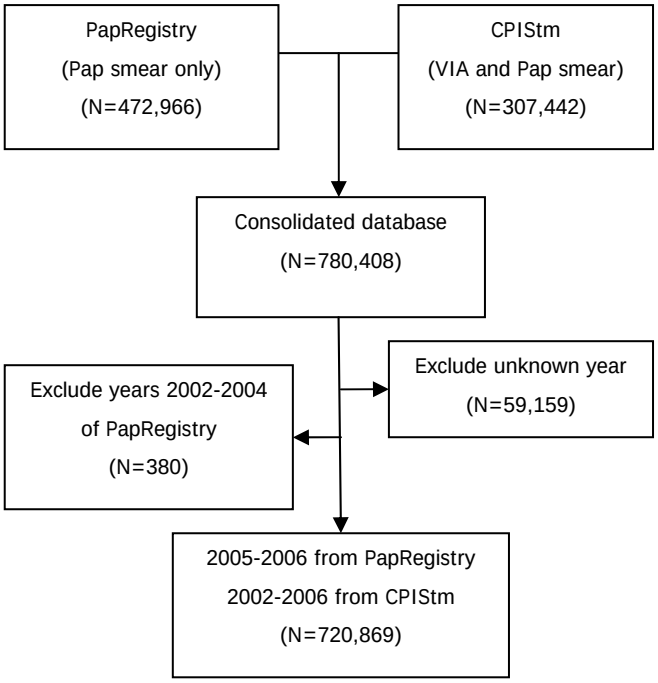
By geographic regions, it is noticeable that most of the CPIStm data (66.0%) came from the northeast region which is the first region VIA/SVA has been adopted and implemented. Less than 1% of the records were from the central region since the

VIA/SVA has set its priority on the remote area. Only one province (Lopburi) in the central region has implemented the VIA/SVA program.[5]

Since the CPIStm data also contain information in certain women whose ages were the VIA target but could not be screened by VIA and receive Pap smear instead, there is a need to consolidate the PapRegistry and CPIStm datasets. Each record of CPIStm was linked to that in PapRegistry using the 13-digit unique identification numbers of the Thai citizens to generate a unified dataset. The combined CPIStm-PapRegistry dataset is also useful for examining any repetition of the screening services that may occur either within or across the screening methods over the study period.

Figure 4 shows the result from consolidating the cervical cancer screening data by linking between PapRegistry and CPIStm databases. The combined PapRegistry-CPIStm dataset consists of 780,408 visits in total. For further estimating the population coverage and determining its variation, 59,159 visits with unknown year of the screening services were excluded. In addition, 380 records of Pap smear abnormally recorded for the years 2002-2004 in the PapRegistry were deleted. This leaves 720,869 visits in total to be included in a final analysis of the consolidated dataset.

Figure 4 Consolidation of databases between PapRegistry and CPIStm



1.2.2 Number of visits and cases

Table 5 shows in each year the total number of service encounters (or visits) and the number of women (cases) undergoing Pap smear or VIA during 2002-2006. Data in 2002-2004 generated from CPIStm revealed only about 1% of the cases (of which

[5] According to the NHSO-MOPH agreement, the target women in all 11 districts of Lopburi are eligible to VIA. However, only 4 districts choose to provide VIA screening services.

nearly all were the VIA recipients) had multiple visits over a year. During the last two years (2005-2006), the number of cases having multiple visits increased considerably (3.4% in 2005 and 23.9% in 2006), mostly in the Pap smear recipients.

Table 5 Number of service encounters and women reported screening

Year	Number of visits	Number of cases	Cases with repeated visits	New cases
2002	14,788[a]	14,657[a]	125[c] (0.9%)	14,657[d]
2003	45,397[a]	44,714[a]	677[c] (1.5%)	44,676[d]
2004	62,075[a]	61,358[a]	721[c] (1.2%)	61,345[d]
2005	342,258[b]	330,929[b]	11,353[c] (3.4%)	330,811[d]
2006	256,351[b]	205,917[b]	49,136[c] (23.9%)	205,356[d]
Total	720,869	657,574		656,845[d]

[a] From CPIStm only: most are VIA but some include Pap smear for those not eligible to VIA
[b] From both CPIStm and PapRegistry
[c] Number of women who have repeated visits within the same year regardless of screening methods
[d] Number of women who have their first visit regardless of screening methods during 2002-2006

The rightmost column in Table 5 shows the number of women who had their screening for the first time regardless of screening methods during this five-year period. In sum, the 720,869 visits recorded in the combined PapRegistry-CPIStm dataset belonged to a total of 656,845 women. Disparity in the numbers between the service encounters, the yearly cases and the new cases signals possibility of the repeated screening within a year or over the 5-year period in some women. This requires an account for potential duplication when estimating the true coverage of the national screening program.[6]

1.2.3 Coverage in target population

Table 6 presents the number of the newly screened cases broken down by screening methods, either Pap smear or VIA. In total, more than a half million (640,455) women have their uterine cervix screened by either Pap smear (N=407,478 during 2005-2006) or VIA (N=232,977 during 2002-2006). The Pap smear coverage in the defined target female population is approximately 11% in 2005.[7] During the 2-year (2005-2006) period, the average Pap smear coverage in the target population is only 8.8%. A partly completed report of PapRegistry may explain the lower coverage (6.6%) in 2006.

[6] For those visiting private clinics, the fraction of repeated screening is probably higher. However, health facilities making contracts with NHSO are mostly in the public sector.

[7] The figures cover only those reported by the national screening program which includes mostly the screening services provided by health facilities in public sectors. Nearly all Pap smear cases are obtained from PapRegistry. Those from CPIStm included those ineligible to VIA (such as incomplete SCJ).

Table 6 Population coverage by screening methods

Year	Pap smear			VIA		
	Target	New cases	Coverage	Target	New cases	Coverage
2002	-	(51)[b]	-	148,207[e]	14,606	9.9%[d]
2003	-	(4,903)[b]	-	255,352[e]	39,773	15.6%[d]
2004	-	(11,436)[b]	-	317,408[e]	49,909	15.7%[d]
2005	2,288,253[a]	255,004	11.1%[d]	952,393[e]	75,807	8.0%[d]
2006	2,322,187[a]	152,474	6.6%[d]	1,213,337[e]	52,882	4.4%[d]
Total	4,610,440	407,478[c]	8.8%[d]	1,239,965[f]	232,977	18.8%[d]

[a] Number of women aged 35, 40, 45, 50 ,55, and 60 years in 75 provinces under the NHSO-MOPH contract
[b] Number of women receiving Pap smear, obtained from CPIStm data
[c] Exclude cases in 2002-2004 obtained from CPIStm since PapRegistry has not been implemented until 2005
[d] Number of new cases (regardless of target ages) per number of target population for each screening method
[e] Number of women aged 30-44 years (except 35 and 40 years) in the VIA implemented provinces
[f] Summation of the provincial annual average of target population across 17 VIA provinces

The VIA/SVA program gives quite a different picture. The VIA screening covered approximately 10% of its target population in 2002. This occurred in the first VIA province, Roi-Et in the northeast. Two years later in 2003 and 2004, the population coverage increased to 15.6% and 15.7%, all activities were still in the northeast region. Then in 2005 and 2006, the coverage declined to 8.0% and 4.4%, respectively. Two factors might explain this phenomenon. In 2005, the VIA program was expanded to new provinces in other regions that might intentionally limit the initial-year target by giving a priority to the population living inside the hospital catchment's area (i.e., within district center). For the northeastern provinces that have implemented the VIA program previously, they might have already exhausted the easy target group during the early period, then the hard-to-reach group remained in this later period. In sum, the screened cases have accumulated since 2002 to cover 18.8% of the average population in these 17 VIA provinces.[8]

In terms of the VIA uptake, the number of newly screened women rises dramatically in 2003 with a relative increase of 172.3%. The annual growth rates of the VIA screened cases drop to 25.5% and 51.9% in 2004 and 2005, respectively. The number of new women obtaining VIA reduces by 30.2% in 2006. This might be due to the facts that the provinces that are an early adopter (Roi-Et, Nong Khai, Yasothon) tend to implement the VIA/SVA program in all of their districts, whereas some of the late adopters may be cautious, hence implemented the program in selected districts, hence, scaled down the total number of target population (Table 3).[9]

[8] Notably, only one province (Roi-Et) reached the 5-year period of the VIA program, while other provinces may have the program implemented only for the first couple years.
[9] One province in 2005-2006 (Phitsanulok) and three provinces in 2006 (Srisaket, Ubon Ratchathani, and Mukdaharn) have only one district each that adopted VIA as a screening strategy.

It is noticeable that even though the annual VIA coverage is not higher than the Pap smear coverage, the performance of VIA seems to be better than Pap smear. First, the overall coverage of VIA is larger (18.8% vs. 8.8%). Second, the number of women screened by VIA would be greater than the Pap smear cases when the number of population at risk as reflected by the implementing districts and provinces (186 vs. 800+ districts in 17 vs. 75 provinces for VIA vs. Pap smear, respectively) are taken into account.

There is still a big gap in an estimation of the population coverage of cervical cancer screening between the demand-side, national household survey data (RHS 2006) and the supply-side, national databases (PapRegistry and CPIStm). Apart case inflation from the social desirability bias that may be introduced by the survey respondents to the household survey, the reporting system is limited to only health care facilities in public sectors mostly under the NHSO-MOPH agreement.

2. Variation by women ages

Tables 7 and 8 show respectively the distribution of women screened by Pap smear and VIA in each year according their ages. The cut point is based on the target age criteria as set in the national program under the NHSO-MOPH agreement (see details before the last paragraph of the Introduction Section).

Table 7 Age distribution of women screened by Pap smear, 2005-2006

	2005	2006	Total
35 years	*37,286 (14.6%)*	*24,341 (16.0%)*	*61,627 (15.1%)*
40 years	*41,575 (16.3%)*	*27,552 (18.1%)*	*69,127 (17.0%)*
45 years	*38,834 (15.2%)*	*25,690 (16.8%)*	*64,524 (15.8%)*
50 years	*35,025 (13.7%)*	*24,567 (16.1%)*	*59,592 (14.6%)*
55 years	*26,793 (10.5%)*	*17,451 (11.4%)*	*44,244 (10.9%)*
60 years	*16,161 (6.3%)*	*11,540 (7.6%)*	*27,701 (6.8%)*
Target[a]	195,674 (76.7%)	131,141 (86.0%)	326,815 (80.2%)
Non-target[b]	51,075 (20.0%)	18,662 (12.2%)	69,737 (17.1%)
Other/unknown[c]	8,255 (3.2%)	2,671 (1.8%)	10,926 (2.7%)
Total	255,004 (100%)	152,474 (100%)	407,478 (100%)

[a] Women aged 35, 40, 45, 50, 55, and 60 years
[b] Women at risky ages (30-60 years) not in the national target: 30-34, 36-39, 41-44, 46-49, 51-54, and 56-59 years
[c] Women aged < 30 years or > 60 years or missing record on age

Table 8 Age distribution of women screened by VIA, 2002-2006

	2002	2003	2004	2005	2006	Total
30-34 years	*4,859 (33.3%)*	*12,652 (31.8%)*	*14,789 (29.6%)*	*21,842 (28.8%)*	*14,273 (27.0%)*	*68,415 (29.4%)*
36-39 years	*3,584 (24.5%)*	*9,781 (24.6%)*	*12,654 (25.4%)*	*20,964 (27.7%)*	*15,218 (28.8%)*	*62,201 (26.7%)*
41-44 years	*2,619 (17.9%)*	*7,780 (19.6%)*	*9,888 (19.8%)*	*18,350 (24.2%)*	*14,690 (27.8%)*	*53,327 (22.9%)*
Target[a]	11,062 (75.7%)	30,213 (76.0%)	37,331 (74.8%)	61,156 (80.7%)	44,181 (83.5%)	183,943 (79.0%)
Non-target[b]	2,949 (20.2%)	8,117 (20.4%)	10,466 (21.0%)	12,713 (16.8%)	7,515 (14.2%)	41,760 (17.9%)
Other/unknown[c]	595 (4.1%)	1,443 (3.6%)	2,112 (4.2%)	1,938 (2.6%)	1,186 (2.2%)	7,274 (3.1%)
Total	14,606 (100.0%)	39,773 (100.0%)	49,909 (100.0%)	75,807 (100.0%)	52,882 (100.0%)	232,977 (100%)

[a] Women aged 30-44 years (excluding 35 and 40 years): 30-34, 36-39, and 41-44 years
[b] Women at risky ages (30-60 years) not in the national target: 35, 40, 45, 50, 55, and 60 years
[c] Women aged < 30 years or > 60 years or missing record on age

It is difficult for a health care provider to refuse to provide the screening service to women even they are not in the target age groups. The analysis shows approximately 15-20% of the women receiving the cervical cancer screening were not in the national target ages. This non-target fraction is similar between Pap smear and VIA. However, there is a tendency of increasing share by the target age screening for both Pap smear and VIA.

For the Pap smear target groups, the first four younger age categories (35, 40, 45, and 50 years) each received the screening in a higher fraction (approximately 15-17%) than the last two older categories (55 and 60 years) (approximately 7-10%) (Table 7). This pattern of target age distribution is consistent between 2005 and 2006.

For the VIA target, the number of women shared by the oldest age range (41-44 years) increases overtime from approximately 18% in 2002 to 28% in 2006; whereas the youngest (30-34 years) declines from 33% in 2002 to 27% in 2006 (Table 8).

Tables 9 and 10 present the corresponding population coverage in the target population as stratified by ages. Though Pap smear was performed in the younger women more than the older, the coverage does not follow this trend. Over the two-year period, the Pap smear coverage in 35-year women is the lowest (6.0%), while the highest (7.9%) is found in 50-year women (Table 9). This is because an age structure of the Pap smear target population is in a pyramid shape.

Table 9 Pap smear coverage in target population by age groups, 2005-2006

	2005		**2006**		**Total**	
	Population	**Coverage**	**Population**	**Coverage**	**Population**	**Coverage**
35 years	507,307	7.3%	518,556	4.7%	1,025,863	6.0%
40 years	497,784	8.4%	492,908	5.6%	990,692	7.0%
45 years	438,511	8.9%	434,345	5.9%	872,856	7.4%
50 years	373,600	9.4%	383,814	6.4%	757,414	7.9%
55 years	285,069	9.4%	286,629	6.1%	571,698	7.7%
60 years	185,982	8.7%	205,935	5.6%	391,917	7.1%
Total	2,288,253	8.6%	2,322,187	5.6%	4,610,440	7.1%

Table 10 VIA coverage in target population by age groups, 2002-2006

	2002		2003		2004		2005		2006		Cumulative cases	Final coverage [a]
	Population	Coverage	Population	Coverage	Population	Coverage	Population	Coverage	Population	Coverage		
30-34 years	67,143	7.2%	111,295	11.4%	137,158	10.8%	357,855	6.1%	469,273	3.0%	68,415	14.6%
36-39 years	44,730	8.0%	79,278	12.3%	99,524	12.7%	301,466	7.0%	380,523	4.0%	62,201	16.3%
41-44 years	36,334	7.2%	64,779	12.0%	80,726	12.2%	293,072	6.3%	363,541	4.0%	53,327	14.7%
Total	148,207	7.5%	255,352	11.8%	317,408	11.8%	952,393	6.4%	1,213,337	3.6%	183,943	15.2%

[a] Ratio between cumulative number of women screened during 2002-2006 and number of target population in 2006

The overall VIA coverage during 2002-2006 for the target population (30-34, 36-39, and 41-44) is 15.2% (Table 10). The coverage in the youngest women (14.6% in 30-34 years) is comparable to the oldest counterpart (14.7% in 41-44 years).

3. Variation by geographic regions of health care facilities

There was variation in the population coverage across geographic regions of the health care facilities that provided the cervical cancer screening services. For Pap smear, as much as 35,019 women in total (or 8.6% of all Pap smear cases) were not found the record for health facilities, hence, the region cannot be located. Among those identified region, the Pap smear coverage is highest in the northeast in both years (12.9% in 2005 and 7.9% in 2006) (Table 11). The lowest coverage is found in the central region (7.5% in 2005 and 2.8% in 2006).

Table 11 Pap smear coverage by geographic regions, 2005-2006

	2005		2006		Total	
	Population	Coverage	Population	Coverage	Population	Coverage
Central	641,918	7.5%	650,914	2.8%	1,292,832	5.2%
North	503,525	10.3%	507,283	7.1%	1,010,808	8.7%
Northeast	838,877	12.9%	850,781	7.9%	1,689,658	10.4%
South	303,933	8.6%	313,209	5.0%	617,142	6.8%
Bangkok		22 cases		246 cases		268 cases
Unknown		20,137 cases		14,882 cases		35,019 cases

Table 12 VIA coverage by geographic regions, 2002-2006

	2002		2003		2004		2005		2006	
	Population	**Coverage**	**Population**	**Coverage**	**Population**	**Coverage**	**Population**	**Coverage**	**Population**	**Coverage**
Central									84,058	0.5%
North							317,948	7.0%	431,860	6.5%
Northeast	148,207	9.9%	255,352	15.6%	317,408	13.5%	362,510	11.0%	391,575	4.2%
South							271,935	5.0%	305,844	2.6%

For VIA coverage, table 12 does not present the complete picture of the country since only 17 provinces have implemented the VIA program until 2006. In the central region, only one VIA province (Lopburi) started the program in 2006. The overall (2002-2006) coverage by regions is not estimated since only one province (Roi-Et) has adopted the program for the full five years. Some other provinces have conducted the VIA programs for couple years. Table 13 presents the number of VIA target population by years of program implementation. These annual population figures are used for estimating the annual VIA coverage. The provincial average population is then used as the basis for calculating the overall coverage of VIA.

Table 13 Number of target population in provinces implementing VIA program

	2002	2003	2004	2005	2006
Roi-Et	148,207	153,132	151,016	152,810	152,982
Nong Khai	-	99,810	101,316	102,226	102,535
Nakhon Phnom[a]	-	2,410	2,398	2,493	-
Yasothon	-	-	62,678	62,890	63,153
Chiang Mai	-	-	-	206,798	163,524
Utraradit	-	-	-	54,398	53,414
Nan	-	-	-	53,160	52,331
Phitsanulok[a]	-	-	-	3,592	3,490
Amnat Charoen	-	-	-	42,091	41,968
Surat Thani	-	-	-	105,894	107,343
Nakorn Srithamaraj	-	-	-	166,041	156,193
Lopburi[b]	-	-	-	-	84,058
Petchaboon	-	-	-	-	111,845
Tak	-	-	-	-	47,256
Srisaket[a]	-	-	-	-	20,136
Ubon Ratchathani[a]	-	-	-	-	6,755
Mukdaharn[a]	-	-	-	-	4,046
Krabi	-	-	-	-	42,308
Total	148,207	255,352	317,408	952,393	1,213,337

[a] Based on one district that implemented the VIA program
[b] Based on all 11 districts under the NHSO-MOPH contract though 4 districts actually implemented the VIA program

4. Trends in VIA and Pap smear coverage for provinces implementing both VIA and Pap smear

Tables 14 and 15 shed light on the screening uptake and coverage performance for the provinces that have adopted both Pap smear and VIA as their cervical cancer control and prevention strategies. In Roi-Et, five years of the VIA implementation yield the cumulative cases of 82,649 women and the coverage of 54.5% of total target population which are the highest performance of all (Table 14). Two other provinces, Nong-Khai and Yasothon that commenced the VIA program in the second phase (2003-2004) have 36.2% and 40.0% of the population coverage, respectively. Ironically, Nakhon Phnom that conducted a VIA pilot in one district in 2003 rarely performed and decided to withdraw the program in 2006.

Table 14 Trend in VIA coverage for provinces implementing both VIA and Pap smear, 2002-2006

	2002		2003		2004		2005		2006		Average Population	Cum. cases	Final coverage
	Cases	Coverage	Cases	Coverage	Cases	Coverage	Cases	Coverage	Cases	Coverage			
Roi-Et	14,586	9.8%	23,748	15.5%	15,414	10.2%	19,774	12.9%	9,127	6.0%	151,629	82,649	54.5%
Nong Khai			14,519	14.5%	13,254	13.1%	7,339	7.2%	1,631	1.6%	101,472	36,743	36.2%
Nakhon Phnom[a]			(1)		(1)		(3)		(2)		2,434	7	0.3%
Yasothon			(748)		10,902	17.4%	8,403	13.4%	5,130	8.1%	62,907	25,183	40.0%
Chiang Mai			(1)		(2)		10,172	4.9%	12,127	7.4%	185,161	22,302	12.0%
Utraradit					(3)		7,689	14.1%	4,096	7.7%	53,906	11,788	21.9%
Nan	(1)				(1)		3,834	7.2%	5,247	10.0%	52,746	9,083	17.2%
Phitsanulok[a]							880	24.5%	453	13.0%	3,541	1,333	37.6%
Amnat Charoen			(796)		(3,393)		4,473	10.6%	611	1.5%	42,030	9,273	22.1%
Surat Thani			(1)		(6,925)		10,049	9.5%	3,026	2.8%	106,619	20,001	18.8%
Nakorn Srithamaraj	(1)				(44)		3,834	2.3%	2,097	1.3%	161,117	5,976	3.7%
Lopburi[b]									433	0.5%	84,058	433	0.5%

	2002		2003		2004		2005		2006		Average Population	Cum. cases	Final coverage
	Cases	Coverage	Cases	Coverage	Cases	Coverage	Cases	Coverage	Cases	Coverage			
Petchaboon			(2)		(4)		(12)		4,312	3.9%	111,845	4,330	3.9%
Tak			(1)				(4)		1,910	4.0%	47,256	1,915	4.1%
Srisaket[a]	(1)		(1)		(2)		(6)		(2)		20,136	12	0.1%
Ubon Ratchathani[a]	(1)		(2)		(8)		(7)		(7)		6,755	25	0.4%
Mukdaharn[a]	(1)		(1)		(2)		(0)		(1)		4,046	5	0.1%
Krabi							(6)		2,843	6.7%	42,308	2,849	6.7%

[a] Based on one district that implemented the program
[b] Based on all 11 districts adopting the NHSO-MOPH contract though 4 districts actually implemented the program

The coverage in the third-phase provinces that started the VIA program in 2005 ranges from 12.0% to 22.1%, except in Nakorn Srithamaraj in the south (3.7%) and in one district of Phitsanulok in the north (37.6%). The provinces that implemented the program last year (2006) have a relatively low coverage. Three provinces in the northeast, including Srisaket, Ubon Ratchathani, and Mukdaharn and one in the central region (Lopburi) reported abnormally few VIA cases.

Notably, the provinces that performed quite well on the VIA coverage also showed the above average performance on Pap smear screening. An exception includes Phitsanulok and Amnat Charoen of which the Pap smear coverage is only 0.1% and 6.3%, respectively (Table 15).

Table 15 Trend in Pap smear coverage for provinces implementing both VIA and Pap smear, 2005-2006

	2005		2006		Total		
	Cases	Coverage	Cases	Coverage	Population	Cases	Coverage
Roi-Et	10,172	19.2%	6,536	12.0%	107,368	16,708	15.6%
Nong Khai	10,992	32.8%	4,276	12.3%	68,171	15,268	22.4%
Nakhon Phnom	5,215	19.9%	4,019	14.9%	53,089	9,234	17.4%
Yasothon	6,806	31.2%	2,278	10.2%	44,092	9,084	20.6%
Chiang Mai	7,113	10.5%	7,803	11.3%	136,374	14,916	10.9%
Utraradit	3,019	14.5%	1,742	8.3%	41,946	4,761	11.4%
Nan	4,304	21.6%	3,329	16.6%	39,933	7,633	19.1%
Phitsanulok	30	0.1%	71	0.2%	72,363	101	0.1%
Amnat Charoen	1,680	11.8%	150	1.0%	28,896	1,830	6.3%
Surat Thani	9,228	26.4%	4,949	13.7%	71,151	14,177	19.9%
Nakorn Srithamaraj	8,010	14.6%	1,053	1.9%	110,309	9,063	8.2%
Lopburi	13,789	43.0%	2,179	6.7%	64,364	15,968	24.8%
Petchaboon	10	0.0%	2,359	5.8%	81,966	2,369	2.9%
Tak	1,015	6.0%	190	1.1%	34,479	1,205	3.5%
Srisaket	2,035	3.7%	2,698	4.9%	109,784	4,733	4.3%
Ubon Ratchathani	710	1.1%	3,441	5.2%	131,536	4,151	3.2%
Mukdaharn	866	7.0%	1,641	12.7%	25,221	2,507	9.9%
Krabi	948	7.2%	584	4.2%	27,187	1,532	5.6%

The provinces that just adopted VIA in 2006 and had l relatively low VIA coverage also show a below-average of Pap smear coverage. One exception is in Lopburi. Even though the VIA coverage is only 0.5% (only 4 out of 11 districts actually implemented the program), its performance on the Pap smear coverage is as high as 24.8%.

Finding like this suggests that the VIA uptake does not occur at the expense of Pap smear probably because their targets have been set as a complement rather than a substitute. Health managers and facilities in the provinces that are very proactive in VIA also actively engage in Pap smear implementation.

5. Variation by health care facilities

Distribution in the number of women screened by Pap smear and VIA by health care facility types is shown in tables 16 and 17, respectively. Pap smear was performed mostly at the sub-district health centers (66.0%). District hospitals and other facilities provide Pap smear services for a minor fraction of the women.

Table 16 Health facility distribution of Pap smear visits, 2005-2006

	2005	2006	Other years	Unknown	Total
Health center	171,766 (65.5%)	132,266 (65.3%)	280 (41.1%)	35,743 (71.5%)	340,055 (66.0%)
District hospital	40,772 (15.6%)	28,662 (14.2%)	171 (25.1%)	5,231 (10.5%)	74,836 (14.5%)
Other govt. hospital[a]	13,418 (5.1%)	10,609 (5.2%)	1 (0.1%)	1,086 (2.2%)	25,114 (4.9%)
Other health facility[b]	1,707 (0.7%)	1,036 (0.5%)	0 (0%)	39 (0.1%)	2,782 (0.5%)
Private hospital and clinic	13,792 (5.3%)	9,148 (4.5%)	43 (6.3%)	4,050 (8.1%)	27,033 (5.2%)
Not specified	20,682 (7.9%)	20,784 (10.3%)	187 (27.4%)	3,836 (7.7%)	45,489 (8.8%)
Total	262,137 (100%)	202,505 (100%)	682 (100%)	49,985 (100%)	515,309 (100%)

This distribution pattern is consistent between 2005 and 2006. In addition, a major share of the Pap smear service by health centers is corresponding to the area designated for public health system. Health promotion and disease prevention programs in the sub-districts located outside the district centers are usually responsible by health centers which account for over 8,000 units. The 800+ district hospitals take care of this community-based service only for population living inside district centers or the inner sub-districts. The skill required for smearing and slide fixation is not that difficult for health workers in health centers at the sub-district level to perform. Then if the slide reading and interpretation by cytologists was able to follow shortly and completely, the health center would be an indispensable strategic knob for expanding the Pap smear program.

Even though the screening by private sectors was believed to be under-reported by PapRegistry, 27,033 women screened by private hospitals and clinics found in this analysis are quite a number. If the unspecified codes (N=45,489) in table 16 tend to belong to health facilities outside public sectors, then the overall coverage for Pap smear might not be that too low for the reality. For VIA, nearly all cases (97.4%) were screened at the DHS level, whereby health centers and district hospitals share a similar volume (47.6% vs. 49.8%, respectively) (Table 17).

Table 17 Health facility distribution of VIA visits, 2002-2006

	2002	2003	2004	2005	2006	Other years	Total
Health center	5,719 (38.8%)	19,446 (48.2%)	30,029 (59.4%)	38,214 (47.7%)	20,968 (38.9%)	3,940 (44.4%)	118,316 (47.6%)
District hospital	9,018 (61.2%)	20,297 (50.3%)	19,923 (39.4%)	40,065 (50.0%)	30,921 (57.4%)	3,522 (39.7%)	123,746 (49.8%)
Other govt. hospital[a]	0	152 (0.4%)	245 (0.5%)	1,141 (1.4%)	1,238 (2.3%)	1 (0.01%)	2,777 (1.1%)
Other health facility[b]	0	455 (1.1%)	297 (0.6%)	100 (0.1%)	13 (0.02%)	0	865 (0.3%)
Private hospital and clinic	0	0	27 (0.1%)	598 (0.7%)	706 (1.3%)	0	1,331 (0.5%)
Not specified	0	1 (0.002%)	0	3 (0.004%)	0	1,409 (15.9%)	1,413 (0.6%)
Total	14,737 (100%)	40,351 (100%)	50,521 (100%)	80,121 (100%)	53,846 (100%)	8,872 (100%)	248,448 (100%)

[a] Provincial hospital, other MOPH hospital, university hospital, and other Non-MOPH hospital
[b] Provincial health office, Health technical center, nursing/public health college

District hospital share of VIA cases went down in 2003 and 2004, then up again in 2005 and 2006. This reveals one of the major limitations in scaling up the VIA screening towards the hard-to-reach areas. Since the screening technique requires a relatively high skill of at least the registered nurse level, an initiation of VIA tends to limit within the hospital catchment's area (i.e., static service at the hospital in the district center).[10] In some provinces, the district hospitals might play a proactive role by expanding the mobile screening service through health centers at the sub-district level.

6. Screening results

Apart from the overall screening coverage in the population and variations with respect to screening recipients, geographic regions, and health care facilities, performance of the national cervical cancer prevention and control program is determined through the end-results. These include the detection rate and positive test finding, for example.

Table 18 shows the performance of Pap smear screening in three aspects. First, quality of the sample smearing and slide preparation was reported. Second, how well the slide samples from health care providers were matched with those from cytologists was assessed. Third, the incidence of cytologic abnormalities as interpreted by the cytologists was reported.

Table 18 Pap smear screening results

	2005	2006	Other year	Unknown	Total
Total	234,866	187,681	434	49,985	472,966
Slide quality					
Not reported	49,130	12,829	199	18,203	80,361
Reported	185,736	174,852	235	31,782	392,605
Unsatisfactory	1,681 (0.9%)	1,172 (0.7%)	5 (2.1%)	222 (0.7%)	3,080 (0.8%)
Satisfactory	184,055	173,680	230	31,560	389525
Slide matching					
Not assessed[a]	22	12	0	2	36
Assessed	234,844	187,669	434	49,983	472,930
Unmatched	50,954 (21.7%)	13,997 (7.5%)	205 (47.2%)	18,484 (37.0%)	83,640 (17.7%)
Matched	183,890	173,672	229	31,499	389,290
Test result					
Slide unmatched	50,954	13,997	205	18,484	83,640
Found	183,912	173,684	229	31,501	389,326
Not interpreted[a]	22	12	0	2	36
Interpreted	183,890	173,672	229	31,499	389,290

[10] The VIA providers have to be trained intensively for two weeks using a competency-based module. The module requires a qualified nurse as the trainee since this service includes not only a visual inspection of cervix with acetic acid (VIA) itself but also a pelvic examination and further cryosurgery treatment. In Thailand, it is uncommon to have the registered nurses working full time in the sub-district health centers.

	2005	2006	Other year	Unknown	Total
Abnormal	3,888 (2.1%)	2,767 (1.6%)	0	686 (2.2%)	7,341 (1.9%)
Normal	180,002	170,905	229	30,813	381,949

[a] Other malignancy found

A total of 472,966 service encounters recorded for Pap smear was analyzed for the screening performance towards end results. As much as 17.0% (N=80,361) was not found the report on the quality of the slide preparation from the initial health care providers. Only 0.8% of the slides was reported an unsatisfactory quality by the cytologists.[11] The rest was the slides of which the preparation quality was adequate for further reading.

The missing slide is a typical concern for the continuity of Pap smear service. On average, 17.7% of the slides prepared by initial health care providers could not be found for reading and interpretation by the cytologists. The proportion of unmatched slides identified in 2005 is as high as 21.7%, then declined dramatically to 7.5% in 2006. Whether this problem is due to the actual physical loss of slides or the incorrect records in PapRegistry is not known. A decreasing trend in the unmatched slides probably reflects an improvement of the recording and reporting system.
For the interpretable test results (i.e., excluding other types of malignancy found), 1.9% of the slides was determined as epithelial abnormalities.[12] The trend in this abnormality dropped slightly from 2.1% in 2005 to 1.6% in 2006. However, the slides with an unknown year of service show 2.2% as the abnormality test finding.

Of 307,442 service encounters obtained from CPIStm database, 12.4% could not perform VIA because SCJ was not completely visible (Table 19). The fraction of those who came to seek VIA but had the incomplete SCJ is quite stable over time, except very low in the first year (2002). Others might change their minds at the service encounter and choose not to take VIA voluntarily. Those who received Pap smear instead account for 19.2% of the initial VIA-intent visits, on average, with an increasing trend from 11.1% in 2003 to 25.4% in 2005 and 21.6% in 2006.

[11] An unsatisfactory rate of the quality of the prepared slides in Finland (0.01%), US (0.6%), and the Netherlands (1.0%) was reported. If the unreported quality from this analysis was ignored, the slide quality in Thailand was considered within an acceptable limit (i.e., less than 1%).
[12] The high end was reported in UK (6.4%), US (6.4%), and Finland (7.3%), whereas the low end was in the Netherlands (2.3%) and Sweden (1.5%). In Thailand, a university hospital 'Ramathibodi' reported the positive rate of 2.23%. A relatively lower detection rate in Thailand, as compared with certain developed countries does not imply a less severe problem. Instead, it might signal an under-representation of the high risk population on accessibility to the screening.

Table 19 VIA screening results

	2002	2003	2004	2005	2006	Other	Total
Total	14,788	45,397	62,075	107,392	68,670	9,120	307,442
Incomplete SCJ	168 (1.1%)	6,445 (14.2%)	8,646 (13.9%)	12,813 (11.9%)	9,829 (14.3%)	250 (2.7%)	38,151 (12.4%)
Complete SCJ	14,620	38,952	53,429	94,579	58,841	8,870	269,291
Pap smear	51 (0.3%)	5,046 (11.1%)	11,554 (18.6%)	27,271 (25.4%)	14,824 (21.6%)	248 (2.7%)	58,994 (19.2%)
VIA	14,737	40,351	50,521	80,121	53,846	8,872	248,448
VIA test result							
Not interpreted	122	388	302	312	152	17	1,293
Interpreted	14,615	39,963	50,219	79,809	53,694	8,855	247,155
Positive	597 (4.1%)	1,695 (4.2%)	1,693 (3.4%)	3,093 (3.9%)	2,580 (4.8%)	731 (9.0%)	10,389 (4.2%)
Negative	14,018	38,268	48,526	76,716	51,114	8,124	236,766
Following treatment							
Referred	42 (7.0%)	384 (22.7%)	603 (35.6%)	849 (27.4%)	886 (34.3%)	197 (26.9%)	2,961 (28.5%)
Cryotherapy	555 (93.0%)	1,309 (77.2%)	1,075 (63.5%)	2,210 (71.5%)	1,684 (65.3%)	533 (72.9%)	7,366 (70.9%)
Other/Unknown	0	2	15	34	10	1	62

The positive (Aceto-white) rate of VIA is 4.2% on average. The VIA-positive rate dropped slightly in 2004 and 2005, then increased to 4.8% in 2006. Among these positive findings, nearly all underwent the treatment. About one-third (28.5% on average) of the women have been referred to a higher level of care, for example provincial hospitals for further cryotherapy or other appropriate treatments. The referral rate went up to 35.6% in 2004 and down to 27.4% in 2005, then rose again to 34.3% in 2006. Majority of the VIA positive cases (70.9%) still confined to the SVA concept, i.e., received the cryotherapy immediately after the VIA screening. The SVA occurred in as much as 93% of the positive cases in 2002 in Roi-Et.

7. Case study in three provinces

This part will be completed in the final report.

Appendix 2

Work package 2.1: The systematic review of methodologies that have been used in study of economic evaluation of prevention and control of cervical cancer, focusing on characteristics of decision analytic model.

Introduction

There have been substantial advances in understanding of the epidemiology of cervical carcinogenesis and the causal role of oncogenic human papillomavirus (HPV) [9]. Cervical cancer is highly preventable through cytology screening program that facilitate the detection and treatment of pre-cancerous lesions [10]. Alternative methods, such as DNA testing for HPV and simple visual screening may be beneficial when incorporated into the new strategies. Recently, HPV vaccine has been commercial available and HPV vaccination program showed cost-effectiveness [11]. Model-based economic evaluations are a useful tool to generate reliable and relevant information to guide health policy choices of prevention and control cervical cancer. Different types of mathematical models as well as model parameters with expected values of the population under study are crucial to be chosen to accommodate the complexity of the decision.

Objective

The aim of the study was to overview methodologies that have been used in study of economic evaluation of prevention and control of cervical cancer, focusing on characteristics of decision analytic model.

Methods

Searching

The Ovid (Medline) electronic database from 1996 to 2006 was searched, using the key search words of; 1) MeSH term "Uterine Cervical Neoplasms" with subheading "prevention & control", 2) MeSH term "Models, Economic", and 3) keywords "economic evaluation" or "cost effectiveness" or "cost utility" or "cost benefit". The search strategy was: #1 and (#2 or #3), limited to English language. Seventy-eight articles were retrieved.

Selection

The abstracts were reviewed. Selected articles must meet all of the following criteria.

1. Study of prevention and control of cervical cancer
    a. Primary prevention: HPV vaccine program or
    b. Secondary prevention: Cervical cytology screening program with PAP smear, liquid-based cytology (LBC) or HPV DNA testing
2. Study of economic evaluation: Measuring both of costs and outcomes
3. Model based study: Makov model, decision tree or mixed model

Excluded conditions were review articles, letters, or comments. There were 22 articles satisfying the criteria that were detailed in appendix 1 [12-34]. Full-texts of those

studies were retrieved, reviewed and extracted for relevant data including type of economic evaluation, setting and study population, characteristics of decision analysis model, program strategy and its comparator, perspective, and sensitivity analysis. Model parameters that had great impact on the results were summarized.

Results

Study type of economic evaluation

There were 18 studies of cost-effectiveness analysis (CEA), 2 studies of cost-utility analysis (CUA) and 2 studies of both CEA and CUA.

Study setting

Seventeen studies were undertaken in the USA (13 studies) and UK (5 studies). There was one study undertaken in those 5 countries of Thailand, Kenya, Peru, South Africa and India. One study was undertaken in 13 EU countries. Each study was undertaken in Japan, Hong Kong, and South Africa respectively.

Health technology

Nineteen studies involved a variety of cervical cancer screening technologies including visual inspection with acetic acid (VIA), HPV DNA testing, and various types of cytology technology such as Pap smear and liquid based cytology (LCB). The screening strategies were differentiated according to numbers of visits, frequency of screening, targeted ages and diagnostic consequences of screening results such as colposcopy. The comparator in the setting of developing countries was no screening program or opportunistic screening program whereas either current screening practice or hypothetical no-screening strategy was the comparator in the setting of developed countries.

There was one study evaluated HPV vaccination program alone. Two studies evaluated strategies consisting of screening program and HPV vaccination program.

Decision analytic model

Only one study was performed with alongside randomized control trial (RCT) economic evaluation. Fifteen studies clearly documented types of decision analytic models in the economic evaluation; 14 studies of Makov model, and one study of decision tree but the rest of the studies have not provided enough detail. State transitional models were designed to simulate the natural history of the cervical cancer and assess the impact of various preventive or therapeutic interventions.

Markov model characteristics

Health states

Health states in Makov model were mutually exclusive states and were based on histopathology. Different heath states were used from study to study but they could be grouped into 5 main categories. Those main health states consisted of normal health state (no HPV infection or no pre-cancerous stage of cervical cancer), HPV DNA

status (high-risk versus low risk types of HPV DNA), pre-cancerous stage (cervical neoplasia), cancerous stage and death (from cervical cancer or from other etiologies). Diagrams of the models were shown in appendix 2. Biopsy-confirmed pre-cancerous stage was defined as cervical intraepithelial neoplasia (CIN) 1, 2 and 3. Most of the models classified pre-cancerous stage as CIN1 and CIN 2-3. Cytology results of cervical neoplasia could be classified using the new Bethesda classification system as low-grade squamous intraepithelial lesion (LSIL) and high type of squamous intraepithelial lesion (HSIL). Invasive cervical cancer stages were defined using staging system of the Surveillance, Epidemiology, End Results (SEER) program of the National Cancer Institute (local, regional and distant) or the staging system of the Federation Internationale de Gynecologie et d'Obstetrique (FIGO) system (stage 1, 2, 3, and 4).

Health states from normal to pre-cancerous stage were reversible whereas health states of invasive cervical cancer were irreversible. There were 2 studies incorporating HIV status into the models since high prevalence of HIV infection was documented in the study setting (South Africa). Most studies omitted health state of death in the diagrams of their Makov models.

Time horizon and cycle time

Time horizons in most models were lifetime or until 80-85 years. Cycle duration of the model was monthly in 4 studies, every 6 months in 2 studies and yearly in 4 studies. Some studies did not detail time horizon and cycle time.

Perspective

Nine studies used societal perspective whereas 12 studies used third-party perspective in economic evaluation.

Discount rate

Annual discount rates of 3-3.5% were applied for both costs and benefits (effects) in most studies. The maximum discount rates used in the analysis was 7 %.

Model parameters (model inputs)

Model parameters varied from study to study and from model to model. However, the general parameters of the studies that evaluated screening strategy might included age-specific prevalence rates of basic health states, transitional probabilities between health states, screening and diagnostic test characteristics, characteristics of screening program, compliance and coverage of the program, survival and mortality of health states, and costs. Diagnostic test characteristics included sensitivity and specificity of the tests. Characteristics of screening program consisted of age of screening onset, screening interval and number of visits. Mortality, survival and prognosis of each health state depended on diagnostic options following the screening results and treatment options. Cost parameters were classified as direct and indirect cost regarding study perspective. Direct medical costs mainly attributed to treatment of cervical cancer regarding cervical staging. Additional model parameters of the studies that evaluated HPV vaccination program were vaccine efficacy, duration of the efficacy, and characteristics of vaccination program such as age of vaccination and vaccine coverage.

Model validation

Face validation and predicitive validation were used in most studies to check accuracy of the model. National data of age-specific incidences of cervical cancer and mortality rates of the cancer were validated with the figures simulated by the model.

Sensitivity analysis

Sensitivity analysis assessed robustness of the results due to variations in several model inputs. In other words, sensitivity analysis assessed the impact of individual model inputs on the results. Most studies provided uni-variate and multivariate sensitivity analysis. Only one study was undertaken probabilistic sensitivity analysis. Three studies were not undertaken sensitivity analysis.

Parameters had great impact on the results varied from study to study, and from model to model. No unique parameters that had great impact to the overall results could be demonstrated. Four studies reported no obvious parameters that influenced the results by performing multivariate sensitivity analysis.

Discussion and Conclusion

Most studies published after 2000 well clarified characteristics of the decision analytic models and diagrams of the model were shown accordingly. All models simulate the natural of HPV infection and cervical carcinogenesis. The health states in most models incorporate cervical neoplasm status, cancer status and HPV DNA status based on histopathology.

Pattern of prevention and control of cervical cancer strategy has changed from focusing only a variety of cervical cytology screening technologies to incorporating HPV vaccine strategy in economic evaluation study since commercial HPV vaccine has been available in 2003. Most simulation model had the comparator as no screening program in hypothetical situation in developed countries and no organized screening practice in developing countries including Asian countries. Model and strategy assumptions varied from model to model, study to study. The screening strategies were differentiated according to screening technology, numbers of visits, frequency of screening, targeted ages and diagnostic consequences of screening results. Assumption of HPV vaccine technology included age of vaccination, vaccine coverage, its efficacy and duration of efficacy. Model parameters varied from study to study and from model to model because of different technology strategies and different model assumptions.

Some studies documented societal perspective in the analysis but indirect costs were not taken into account [35]. No conclusion of influential parameters to the results can be made from sensitivity analysis of the entire studies because parameters that had great impact of the results varied from study to study and from model to model.

Summary table of model characteristics

Reference	Legood, et al 2006	Goldie, et al 2005	Sherlaw-Johnson, et al 2004	Goldie, et al 2004
Economic type	CEA	CEA	CEA	CUA
Setting	UK	Five countries*	UK	USA
Study population	Women aged 25-64 with borderline or mildly dyskaryotic	women aged from 30 years	Women aged from 15 years	Women over 12 years
Model	Markov model	Markov model	Markov model	Markov model
Health satates	Normal, HPV, CIN1, CIN2-3, Cancer(4), Death	As Goldie, et al 2001	high risk HPV, CIN(1-3), Pre-clinical Cancer, Clinical Cancer (4), Death	Normal, HPV(5), CIN1, CIN2-3, Cancer (3), Death
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime
Cycle length	6-month	1-month	1 year	6-month
Discount rate	Both 3.5% (first 30 years) then 3%	Both 3%	Both 3.5%	Both 3%
Perspective	Provider	Societal	Provider	Societal, but no indirect cost?
Strategies	Screening Strategy (cervical smear involving LCB and HPV testing)	Screening Strategy (numbers of visits, frequency of screening and ages with 3 testing)	Screening Strategy (3 or 5 interval of screening, with and without LBC)	Screening and HPV vaccine (no vaccination and no screening, no vaccination plus screening, and vaccination plus screening)
Comparator	Conventional cytology	No screening	No screening	Current screening
Sensitivity analysis	Univariate sensitivity, A probabilistic sensitivity analysis	Univariate sensitivity analysis	Univariate and multivariate sensitivity analyses	Extensive one way sensitivity analysis
Sensitive parameters from sensitivity analysis	1. costs associated with LCB, HPV testing and colposcopy, 2. Transitional probability of pre-invasive cancer developed to high grade disease, 3.Sensitivity of cytology to detect CIN2-3	1. Costs associated with treatment of invasive cancer, 2. Target age of screening, 3. Test characteristics, 4. Screening costs, 5. Follow-up rates, 6. Screening coverage among women with different risks of cancer	No obvious sensitive paratmeters	1. Duration of vaccine efficacy, 2.The proportion of persistent HPV in women older than 30 years, 3.The underlying frequency of cervical cancer screening, 4.Age at which screening is initiated, and 5.Cost of following women with atypical cytology screening results and low-grade lesions.

Summary table of model characteristics (Cont.)

Reference	Kim, et al 2004	Vogt, et al 2003	Sanders, et al 2003	Kulasingam, et al 2003
Economic type	CEA	CEA, alongside RCT	CEA, CUA	CEA
Setting	Hongkong	USA	USA	USA
Study population	Women over 15 years old.	Unscreened women for more than 3 years	Women over 12 years	Women over 12 years
Model	Markov model	No	Markov model	Markov model
Health satates	Normal, CIN1, CIN2-3, Cancer (3), Death	-	Normal, low-risk HPV, high-risk HPV, SIL, Cancer, Death	Normal, low-risk HPV, high-risk HPV, CIN1, CIN2-3, Cancer(4), Death
Time horizon	Lifetime	12 weeks	Lifetime	Lifetime (85 years)
Cycle length	1-month		1 month	Not stated
Discount rate	Both 3%	No	Both 3%	Both 3%
Perspective	Societal	Provider	Provider	Societal
Strategies	Screening Strategy (Pap, LBC, opportunistic screening , organized screening)	Three interventions to deliver breast and cervical cancer screening	HPV vaccine strategy (with and without vaccine)	Screening and HPV vaccine startegies (vaccine and or following cyto screening)
Comparator	No screening	Not stated	Standard care	No intervention
Sensitivity analysis	Univariate sensitivity analysis	No	Univariate and multivariate sensitivity analyses	One and two way sensitivity analyses
Sensitive parameters from sensitivity analysis	No obvious sensitive paratmeters	-	No obvious sensitive paratmeters	1. Natural history of HPV infection and response to vaccine, 2. The impact of treatment of CIN, 3. The differential impact of a type-specific vaccine on CIN 1 compared with CIN 2-3 and cancer

Summary table of model characteristics (Cont.)

Reference	Mandelblatt, et al 2002	Kim, et al 2002	Goldie, et al 2001	Montz, et al 2001
Economic type	CUA	CEA, CUA	CEA	CEA
Setting	USA	USA	South Africa	USA
Study population	Women over 20 years	Women over 13 years	Women over 30 years	Women over 20 years
Model	Markov model	Markov model	Markov model	Markov model
Health satates	Normal, HPV+LSIL, HPV+HSIL, Cancer+HPV (3), Death	Normal, HPV(detectable), HPV(undetectable) CIN1, CIN2-3, Cancer(3), Death	Normal, HPV, HIV, LSIL, HSIL, Cancer(3), Death	false positive, false negative, true positive, true negative, CIN 1-3, CIS, Cancer, Death
Time horizon	Lifetime	Lifetime	Lifetime	Lifetime (80 years)
Cycle length	1 year	Not stated	1 month	1 year
Discount rate	Both 3%	Both 3%	Both 3%	Both 3%
Perspective	Societal	Societal	Societal	Provider
Strategies	Screening Strategy (Pap, HPV test and combination)	Screening Strategy	Screening Strategy (DVI, HPV testing, Pap, number of visits)	Screening Strategy (LBS, CPS)
Comparator	No screening	No screening	No screening	Usual care
Sensitivity analysis	One and two way sensitivity analyses	Univariate and multivariate sensitivity analyses	Univariate and multivariate sensitivity analyses	Univariate sensitivity analysis
Sensitive parameters from sensitivity analysis	1. HPV test costs, 2. Sensitivity of HPV testing, 3. prevalence of LSIL	No obvious sensitive paratmeters	1. Natural history of SIL, 2.Sensitivity of screening tests 3.Cost of screening tests, 4. Cost of cancer care, 5. HPV prevalence	Little change for Compliance rate of screening

Summary table of model characteristics (Cont.)

Reference	Taylor, et al 2000	Van Ballegooijen, et al 2000	Raab, et al 1999	Brown, et al 1999	Radensky, et al 1998
Economic type	CEA	CEA	CEA	CEA	CEA
Setting	USA	13 EU countries	USA	UK, USA	USA
Study population	Women over 18 years	Unclear	No detail	Women over 20 years	Women over 20 years
Model	Markov model and Decision tree	MISCAN simulation model	Decision analytic model	Mokov model, (Eddy)	Mokov model, (Eddy)
Health satates	Normal, ASCUS, LSIL, HSIL, Cancer, Death	Not stated	Not stated	Not stated	Not stated
Time horizon	18-64 years	Not stated	Not stated	Not stated	Not stated
Cycle length	1 year	Not stated	Not stated	Not stated	Not stated
Discount rate	Both 3%	Not stated	cost-no, effect-5%	Both 3%	Both 3%
Perspective	Societal	Not stated	Provider	societal?,no indirsct cost	Provider
Strategies	Screening Strategy (Pap, PPS)	Not stated	Screening strategy	Screening Strategy (Pap, Thin prep, Autopap, Papnet)	Screening strategy (INNA rescreening)
Comparator	Not stated	Not stated	No screening	Pap smear, 10% rescreen	Unassisted manual screening
Sensitivity analysis	One way sensitivity analysis	No	One way sensitivity analysis	One way sensitivity analysis	One way sensitivity analysis
Sensitive parameters from sensitivity analysis	1. Prevalence of abnormal screening results	-	1. Cost of smear 2. HSIL rate	1. Risk of developing cervical cancer 2. Estimated TPR of the test and 3. Cost of each technology	Specificty and sensitvity of INNA

Summary table of model characteristics (Cont.)

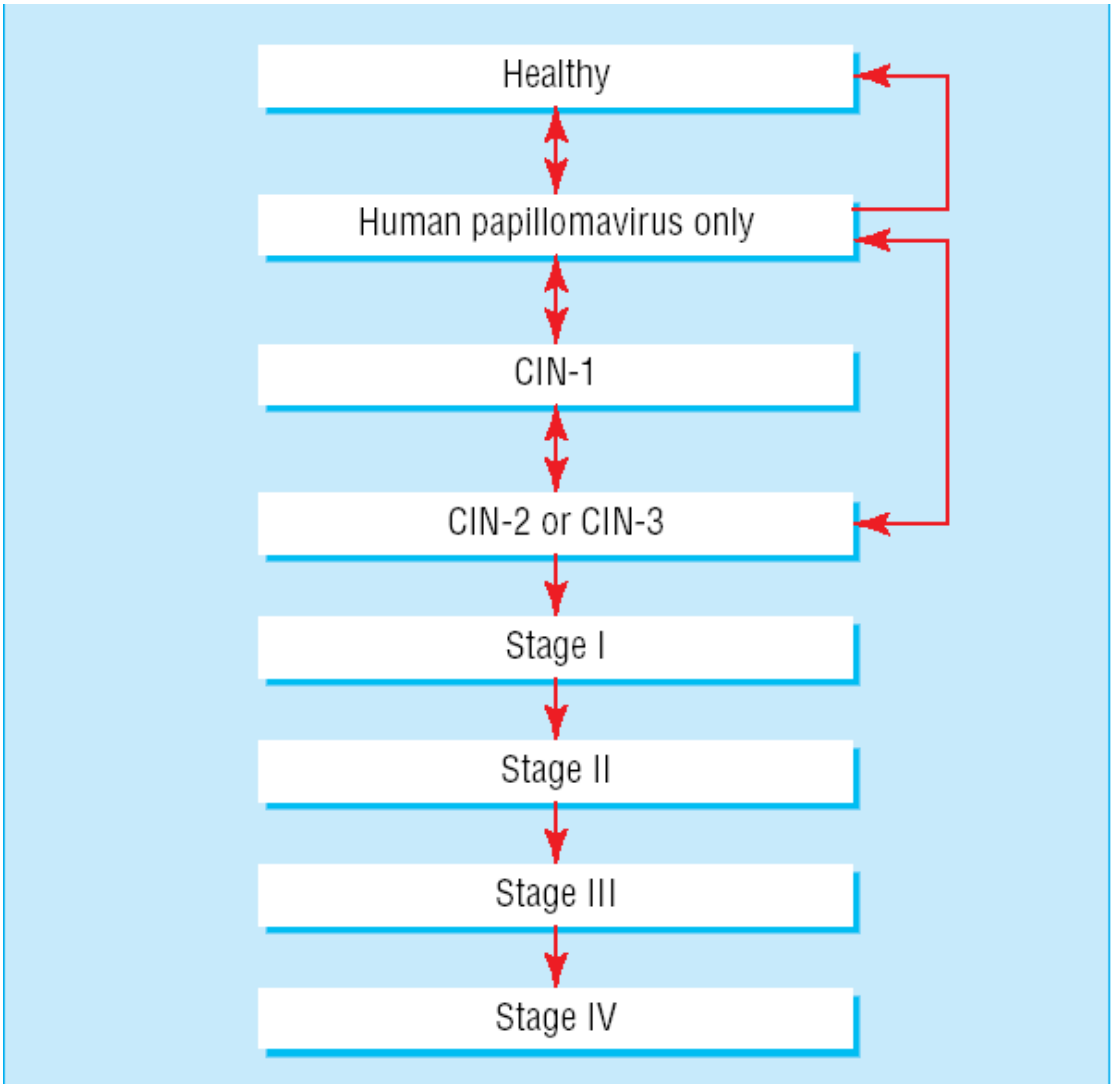
Reference	Matsunaga, et al 1997	Mandelblatt, et al 1997	Waugh N, et al 1996	Waugh N, et al 1996	Schechter, et al 1996
Economic type	CEA	CEA	CEA	CEA	CEA
Setting	Japan	USA	UK	UK	USA
Study population	Women over 30 years	Women over 20 years	Women 20-64 years undergoing cervical screening	Women with no records of a previous smear	Women over >20 years
Model	Decision analytic model	Decision tree	Not stated	Not stated	Makov model
Health satates	Not stated	Cancer, No cancer, Survive, Peri-operative death	Not stated	Not stated	Normal, LSIL,HSIL,Early invasive cancer, Late invasive cancer, Death
Time horizon	Not stated	-	Not stated	Not stated	Not stated
Cycle length	Not stated	-	Not stated	Not stated	Not stated
Discount rate	Both 5%	Both 3%	Both 7%	Both 7%	Both 5%
Perspective	Provider	Provider	Provider	Provider	Provider
Strategies	Screening strategy (Pap screening program)	Emergency room screening	Screening strategy	Screening strategy	Screening strategy (Papnet)
Comparator	No screening program	Routine hospital program	3-year interval screening	No screening	Usual practice
Sensitivity analysis	One way sensitivity analysis	One way sensitivity analysis	One way sensitivity analysis	No	One way sensitivity analysis
Sensitive parameters from sensitivity analysis	1. Screening charge, 2. Incidence rate of cancer (less senitive)	1. The number of women screened, 2. Probability of treatment	-	-	1. Screening interval, 2. Smear quality

Summary table of model characteristics (Cont.)

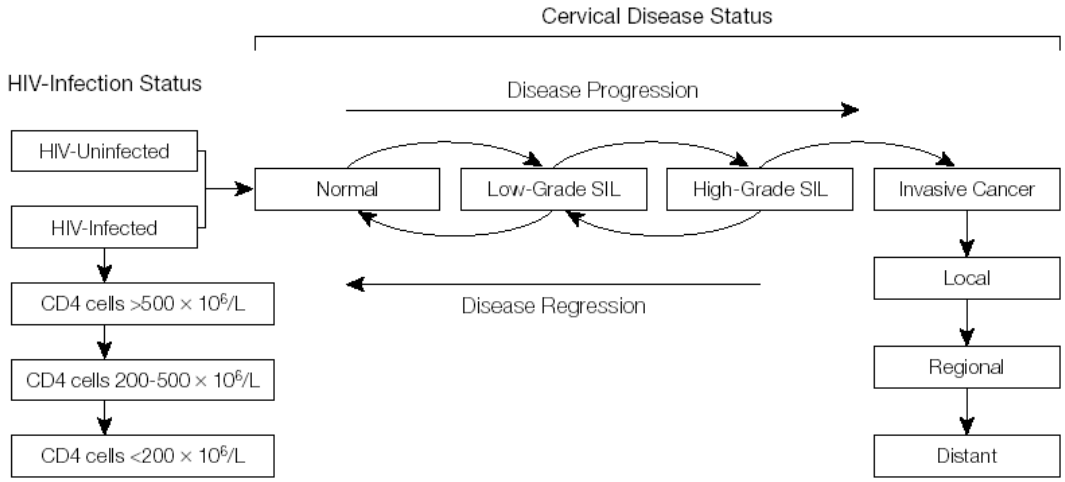
Reference	Mandelblatt, et al 1997	Matsunaga, et al 1997	Waugh N, et al 1996	Waugh N, et al 1996	Schechter, et al 1996
Economic type	CEA	CEA	CEA	CEA	CEA
Setting	USA	Japan	UK	UK	USA
Study population	Women over 20 years	Women over 30 years	Women 20-64 years undergoing cervical screening	Women with no records of a previous smear	Women over >20 years
Model	Decision tree	Decision analytic model	Not stated	Not stated	Makov model
Health satates	Cancer, No cancer, Survive, Peri-operative death	Not stated	Not stated	Not stated	Normal, LSIL,HSIL,Early invasive cancer, Late invasive cancer, Death
Time horizon	-	Not stated	Not stated	Not stated	Not stated
Cycle length	-	Not stated	Not stated	Not stated	Not stated
Discount rate	Both 3%	Both 5%	Both 7%	Both 7%	Both 5%
Perspective	Provider	Provider	Provider	Provider	Provider
Strategies	Emergency room screening	Screening strategy (Pap screening program)	Screening strategy	Screening strategy	Screening strategy (Papnet)
Comparator	Routine hospital program	No screening program	3-year interval screening	No screening	Usual practice
Sensitivity analysis	One way sensitivity analysis	One way sensitivity analysis	One way sensitivity analysis	No	One way sensitivity analysis
Sensitive parameters from sensitivity analysis	1. The number of women screened, 2. Probability of treatment	1. Screening charge, 2. Incidence rate of cancer (less senitive)	-	-	1. Screening interval, 2. Smear quality

Makov model characteristics

Legood R, BMJ 2006



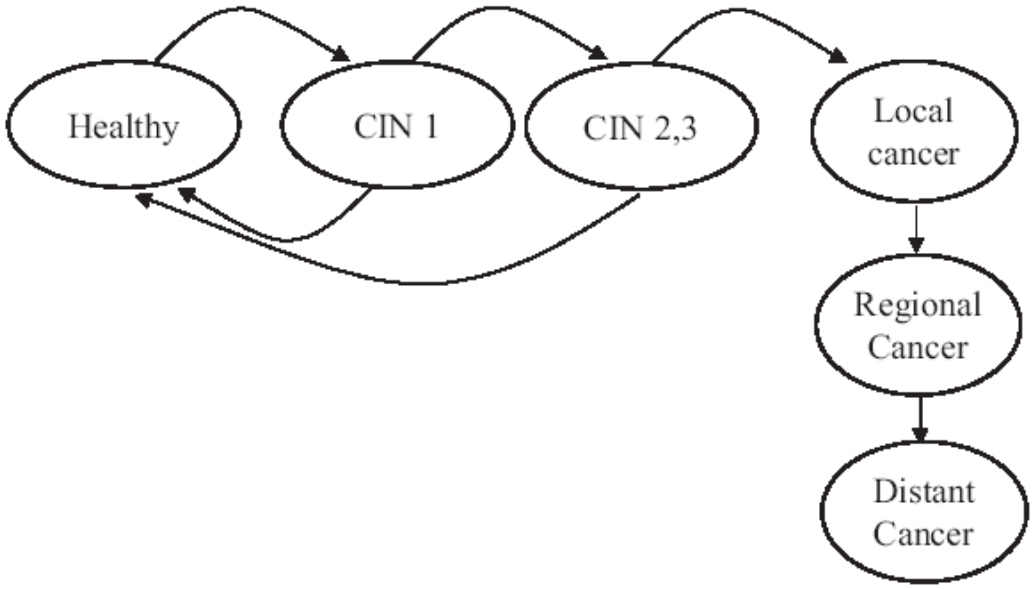
Goldie SJ, New England Journal of Medicine 2005
Goldie SJ, JAMA2001



Health states in the model incorporate cervical disease status, human papillomavirus (HPV) infection status, and human immunodeficiency virus (HIV) infection status. Each month, women can progress or regress in their cervical disease; those at lowest risk of disease progression have no detectable or low-risk HPV DNA and have no HIV infection; those at highest risk of disease progression have detectable high-risk types of HPV DNA and are in later stages of HIV infection. Each month, women who are HIV-infected may progress in their HIV disease. Not shown are women who may die from acquired immunodeficiency syndrome, cervical cancer, or other causes. SIL indicates squamous intraepithelial lesions.

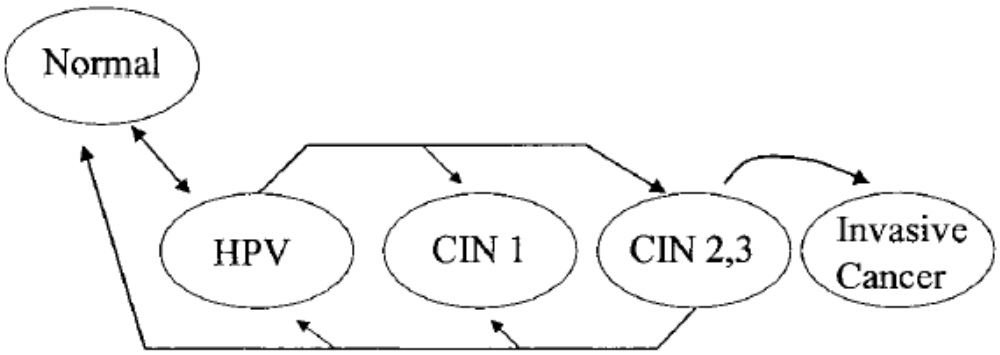
[12]

Kim JJ, Journal of Public Health 2004



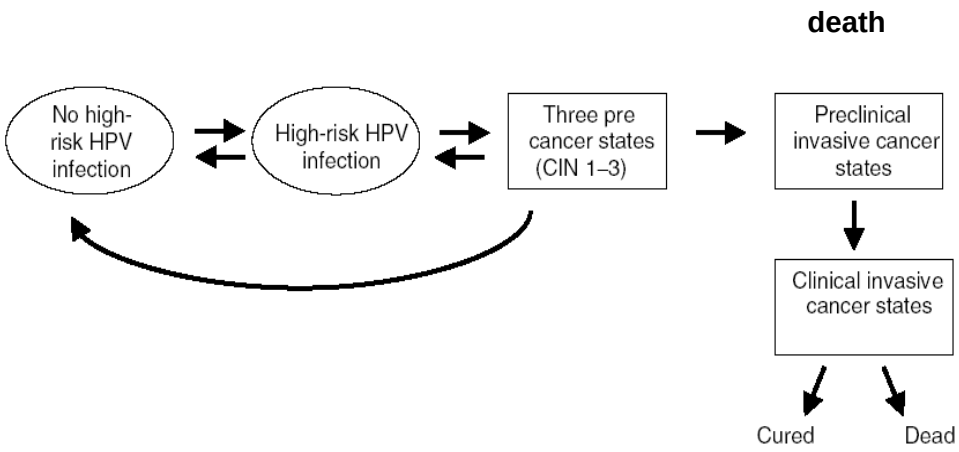
Natural history model. Health states were defined using three categories of cervical health (normal, grade of CIN and stage of invasive cancer). Each month, women face an age-dependent risk of acquiring CIN 1. Women with established cervical lesions can regress to normal, or progress to higher-grade lesions or cervical cancer. Unique health states were defined to distinguish women with prior treatment for CIN and detected cervical disease (through symptoms or screening). Women at any age may die of a cervical cancer-related illness, or other causes.

Goldie SJ, Journal of the National Cancer Institue 2004



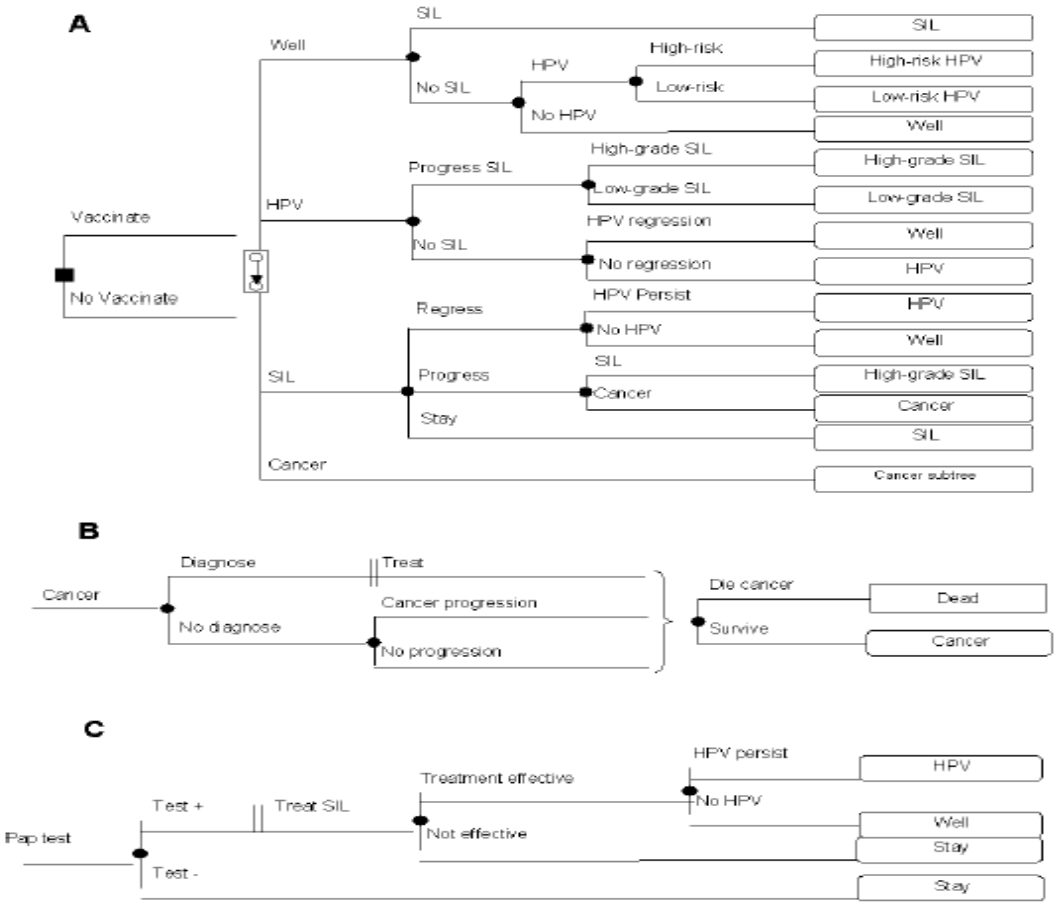
Simple schematic of model. Model simulates the natural history of human papillomavirus (HPV) infection and cervical carcinogenesis while incorporating the underlying type-specific HPV distribution within each stage of cervical disease, by use of a sequence of 6-month transitions among mutually exclusive health states. Health states are defined by use of five general categories of HPV infection (persistent HPV16/18, persistent high-risk non-16/18 HPV types, persistent low-risk HPV types, transient low-risk or high-risk HPV types, and no HPV), three categories of cervical disease (no neoplasia or cancer, cervical intraepithelial neoplasia 1 [CIN1], and cervical intraepithelial neoplasia 2,3 [CIN2,3]), and three categories of invasive cervical cancer (local, regional, and distant). The probabilities governing each of these transitions are conditional on the type of HPV infection. HPV infections may be persistent or transient. Persistent infection with a high-risk type is necessary for invasive cervical cancer. Transient infection with any HPV type may be accompanied by the development of CIN1, and vaccination prior to sexual activity prevents 90% of persistent infection with HPV16/18.

Sherlaw-Johnson C, British Journal of Cancer 2004

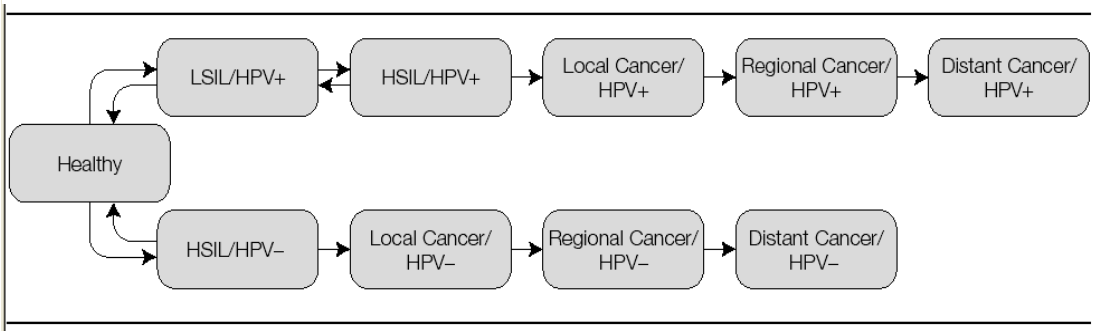


Model representation of disease natural history.

Sanders G D, Emerg Infect Dis 2003

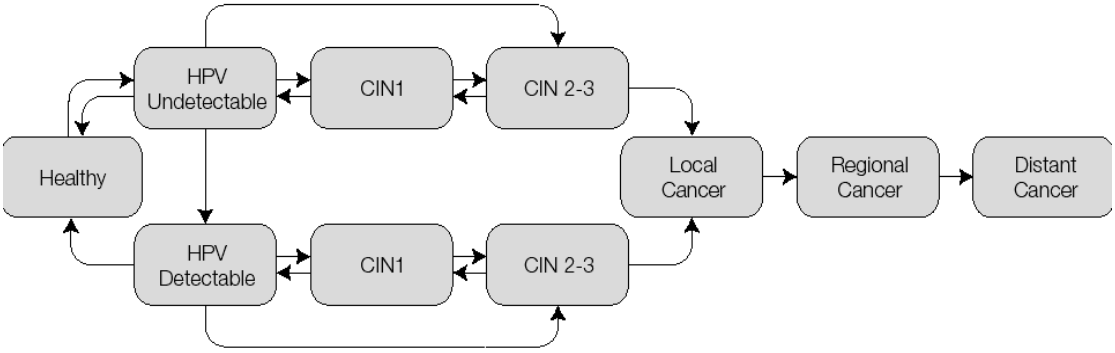


Mandelblatt J S, JAMA 2002



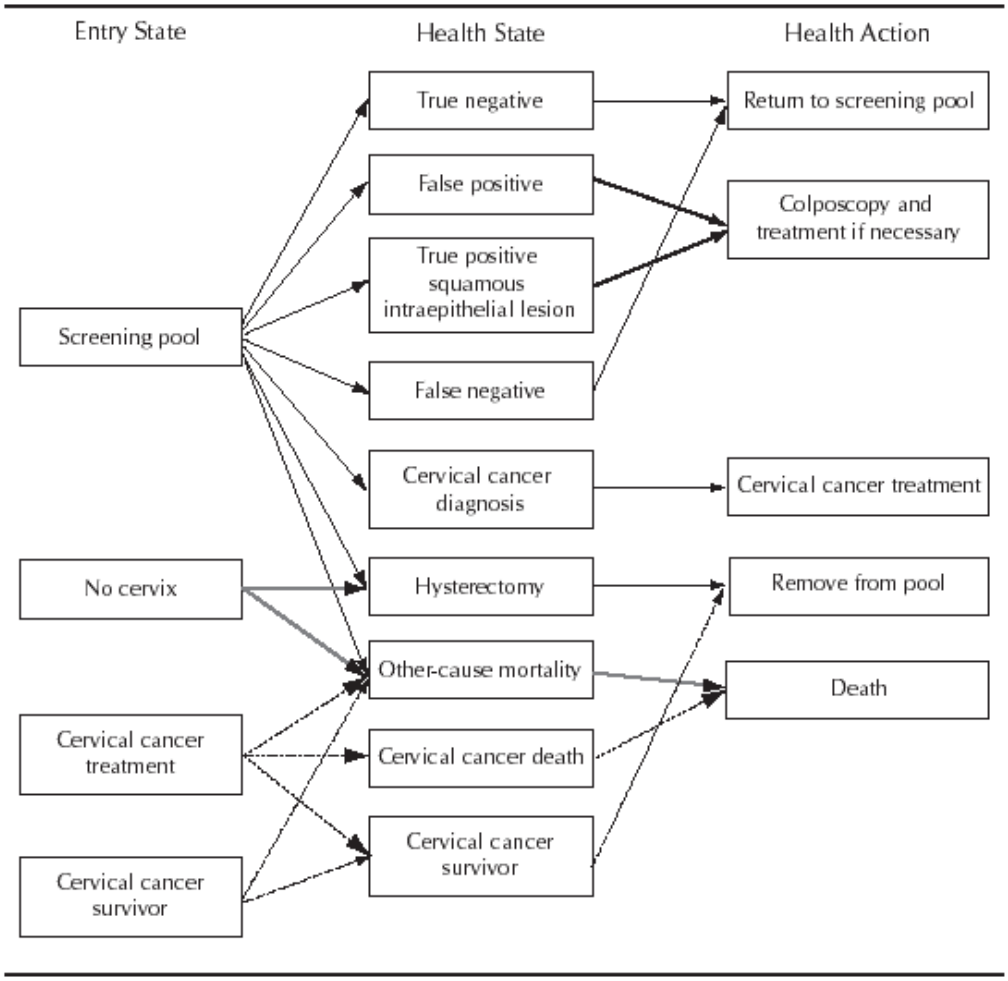
Each circle represents a health state. Not shown are states for human papillomavirus (HPV)-positive and HPV-negative local, regional, and distant cancers that are diagnosed and treated. LSIL indicates low-grade intraepithelial lesion; HSIL, high-grade intraepithelial lesion. Women may have a hysterectomy and no longer be at risk. At any time women can die of cervical cancer or any other cause.

Kim J J, JAMA 2002



Health states were defined using 4 categories of cervical health (normal, infection with human papillomaviru
[HPV], grade of cervical intraepithelial neoplasia [CIN], and stage of invasive cancer). See "Methods" for details

Montz F J, Obstetrics &Gynecology 2001



Movement is from left to right for each cycle to age 65 years.

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Appendix 3

Work package 2.2: The meta-analysis of the efficacy of HPV vaccine

Introduction

There have been substantial advances in understanding of the epidemiology of cervical carcinogenesis and the causal role of oncogenic human papillomavirus (HPV). HPV type 16 an 18 were the most and second most common cause of invasive cancers of the cervix. The availability of HPV vaccine against those oncogenic HPV types has elicited to prevent cervical cancer.

Objective

The aim of the study was to summarize HPV vaccine efficacy in preventing cervical cancer.

Methods

Searching

The Ovid (Medline) electronic database from 1996 to 2006 was searched, using the key search words of MESH term "Papillomavirus vaccines", limited to English language. Twenty five studies were retrieved. The title and abstract of each citation were screened first, and full report was screened second if necessary to select the relevant articles according to selection criteria. Full-texts of those selected studies were retrieved, reviewed and extracted for relevant data.

Selection criteria

Selected studies must meet all of the following inclusion criteria.

1. Design of double blinded randomized controlled trial
2. Studying efficacy of HPV vaccine to prevent cervical cancer
3. Studying both outcomes of pre-cancerous histology lesion and HPV infection

There were 8 studies relevant for reviewing the HPV vaccine efficacy in prevention of cervical cancer [1-8]. Only 4 studies were implemented for quantitative summary measure of efficacy in this meta-analysis. Two studies were excluded because the preparation of only HPV16 L1 virus-like particle has not been available in the market [1,2]. The other two studies were excluded because the extended follow-up of those original studies were already included in this analysis [3,5]. However, the study characteristics of those 8 studies were summarized in table 1.

HPV vaccine and placebo

Three types of HPV vaccine were studied.

1. The quadrivalent vaccine consisted of a mixture of four recombinant HPV type-specific VLPs composed of the L1 major capsid proteins of HPV types 6, 11, 16, and 18 synthesised in Saccharomyces cerevisiae. The dose formulation is comprised of 20 mg of HPV 6 VLP, 40 mg of HPV 11 VLP, 40 mg of HPV

16 VLP, and 20 mg of HPV 18 VLP, formulated with 225 mg of aluminium adjuvant in a total carrier volume of 0.5 ml. The four VLP types were purified and adsorbed onto amorphous aluminium hydroxyphosphate sulphate adjuvant (AAHS).

2. The bivalent HPV-16/18 virus-like particle vaccine (GlaxoSmithKline Biologicals, Rixensart, Belgium) contained 20 g of HPV-16 L1 virus-like particle and 20 g of HPV-18 L1 virus-like particle. Each type of virus-like particle was produced on *Spodoptera frugiperda* Sf-9 and *Trichoplusia ni* Hi-5 cell substrate with AS04 adjuvant containing 500 g aluminum hydroxide and 50 g 3-deacylated monophosphoryl lipid A (MPL, Corixa, Montana, USA) provided in a monodose vial.
3. The HPV16 L1 virus-like particle vaccine (Merck Research Laboratories, West Point, PA) consists of highly purified virus-like particles of the L1 capsid polypeptide of HPV16. The HPV16 L1 polypeptide is expressed in a yeast host (*Saccharomyces cerevisiae*). Virus-like particles are isolated to achieve more than 97% purity and adsorbed onto amorphous aluminum hydroxyphosphate sulfate adjuvant without preservative. The HPV16 vaccine contained 40 g of HPV16 L1 virus-like particle formulated on 225 g of aluminum adjuvant in a total carrier volume of 0.5 ml.

The placebo contained the same adjuvant and was visually indistinguishable from vaccine.

Outcome

The outcomes included both virology (HPV, especially HPV type 16/18) and precancerous pathological endpoints. Persistent HPV infection and precancerous lesion of cervical cancer as CIN2 or worse were key biological intermediates in cervical carcinogenesis. Serious adverse effect and serious adverse effect related to vaccine were also mentioned.

Covariate information

Characteristics of study population (place, eligible criteria, age distribution), vaccine type, administration schedule, duration of follow-up, and study size were included. Population of completed 3-dose vaccination among naive women who had negative results on polymerase-chain-reaction and serologic assays torelevant type of HPV at enrollment was analyzed as per protocol (according per protocol) analysis. Population of at least one dose vaccination was analyzed as intention to treat (ITT) analysis. The ITT1 population included naïve women for HPV infection whereas the ITT2 population included women regardless of HPV infection status..

Definition of accuracy measures and Statistical analysis

Vaccine efficacy was defined as 100% (1-(risk of becoming a case in the vaccine group/risk of becoming a case in the placebo group)). A meta-analysis, yielding a quantitative summary measure of efficacy was implemented. Random-effects models were used for pooling accuracy parameters in cases of statistically significant interstudy heterogeneity (when $P<0.1$ for Cochran's Q test). In the absence of heterogeneity, fixed models were used, with weighting of each individual study

parameter according to reciprocal of its variance [9]. The pooled efficacy was estimated including the 95% confidence intervals (95% CI) according to the type of analysis population and the endpoints of interest. Meta-analyses were performed using the Stata statistical package version 9.0.

Results

The efficacy of the vaccine varied according to the endpoint of interest and type of analysis population. Of total of 15,532 women on per protocol analysis (completed 3-dose vaccination among naïve women), the efficacy of the vaccine was as high as 97.4% (95%CI: 89.5% to 99.4%) according to the outcome endpoint of CIN grade 2 or worse associated with HPV 16/18. The efficacy was 96.2 (95% CI: 90.1% to 98.5%) and low as 40.1 (95%CI: 26.1 to 51.5%) for at least one dose vaccination among naïve women (ITT1 population) and all women regardless of HPV infection status (ITT2 population) respectively. The efficacy was lowest as 16.4% (95% CI: 7.1% to 24.9%) according to the outcome endpoint of CIN grade 2 or worse associated any HPV type of ITT2 population. The meta-analysis results were detailed in table 2, 3 and 4 according to the per-protocol population, the ITT1 population, and the ITT2 population respectively. No obvious serious reaction and serious reaction associated with the vaccine were documented.

Discussion

Histology of CIN grade2 or worse is used as surrogate outcome for cervical cancer prevention in this meta-analysis. Women with histology of CIN grade 2 or worse will be treated and is accepted as pre-cancerous lesion of cervical cancer by the Food Drug and Administration (FDA). Vaccine efficacy is highly effective in preventing HPV16-related and HPV-18 related CIN grade 2 or worse among naïve women who had completed 3-dose vaccination or had incomplete vaccination. However, larger and longer duration of follow-up is needed to verify the efficacy and adverse reaction of the HPV vaccine in preventing cervical cancer. The modest efficacy was found among the entire cohort population regardless status of HPV infection. This may be explained by the apparent lack of efficacy among subjects who had evidence of previous exposure to HPV types included in the vaccine and the contribution of non-vaccine, high-risk HPV types in the public.

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Table 1 Characteristics of the studies

Study (number, author-year)	1. Koutsky, 2002	2. Mao, 2006	3. Harper, 2004	4. Harper, 2006
Country	USA	USA	North America, Brazil	North America, Brazil
Company	Merck Research Laboratories	Merck Research Laboratories	Glaxo SmithKline	Glaxo SmithKline
Vaccine type	HPV16 L1 VLP	HPV16 L1 VLP	HPV16/18 L1 VLP	HPV16/18 L1 VLP
Concentration	40 pg	40 pg	20/20	20/20
Dose	0.5 cc IM	0.5 cc IM	0.5 cc IM	0.5 cc IM
Schedule	0,2,6,month	0,2,6,month	0,1,6 month	0,1,6 month
Age (years)	16-23	16-23	15-25	15-25
key eligible requirement	not pregnant, no prior abnormal pap smear, no more than 5 male sex partners during their lifetime, seronegative	not pregnant, no prior abnormal pap smear, no more than 5 male sex partners during their lifetime, seronegative	not pregnant, no history of an abnormal pap smear, no more than 6 male sex partners during their lifetime, seronegative	not pregnant, no history of an abnormal pap smear, no more than 6 male sex partners during their lifetime, seronegative
Study size	1194 vaccinees, 1198 placebo	1194 vaccinees, 1198 placebo	560 vaccinees, 553 placebo	560 vaccinees, 553 placebo
Duration of follow up	7 months	7 to 48 months	27 months	27 to 53 months
Baseline at day 0				
LSIL	35 vaccinees (4.6%), 34 placebo (4.4%)	35 vaccinees (4.6%), 34 placebo (4.4%)	NA	NA
HSIL	2 vaccinees (0.3%), 4 placebo (0.5%)	2 vaccinees (0.3%), 4 placebo (0.5%)	NA	NA
HPV16 (by PCR)	NA	NA	NA	NA
HPV18 (by PCR)	NA	NA	NA	NA
Serious adverse event	4 vaccinees (0.4%), 3 placebo (0.3%)	NA	22 vaccinees (4%), 19 placebo (3.5%)	16 vaccinees (4%), 19 placebo (5%)
Vaccine related serious adverse event	0 vaccinees, 0 placebo	NA	0 vaccinees, 0 placebo	NA

Table 1 (continue)

Study (number, author-year)	5. Villa, 2005	6. Villa, 2006	7. Garland, 2007	8. FUTURE II study group, 2007
Country	USA, Brazil, Europe	Brazil, Europe	16 countries	13 countries
Company	Merck Research Laboratories	Merck Research Laboratories	Merck Research Laboratories	Merck Research Laboratories
Vaccine type	HPV 6,11,16,18 L1 VLP	HPV 6,11,16,18 L1 VLP	HPV 6,11,16,18 L1 VLP	HPV 6, 11,16,18 L1 VLP
Concentration	20/40/40/20	20/40/40/20	20/40/40/22	20/40/40/21
Dose	0.5 cc IM	0.5 cc IM	0.5 cc IM	0.5 cc IM
Schedule	0,2,6,month	0,2,6,month	0,2,6,month	0,2,6,month
Age (years)	16-23	16-23	16-24	15-26
key eligible requirement	not pregnant, no prior abnormal pap smear, no more than 5 male sex partners during their lifetime	not pregnant, no prior abnormal pap smear, no more than 5 male sex partners during their lifetime	not pregnant, no prior abnormal pap smear, no more than 4 male sex partners during their lifetime **(did not exclude previous HPV infection)**	not pregnant, no prior abnormal pap smear, no more than 4 male sex partners during their lifetime **(did not exclude previous HPV infection)**
Study size	276 vaccinees, 275 placebo	276 vaccinees, 275 placebo	2723 vaccinees, 2732 placebo	6087 vaccinees, 6080 placebo
Duration of follow up	36 months	36 to 60 months	average 36 months	average 36 months
Baseline at day 0				
LSIL	15 vaccinees (5%), 10 placebo (4%)	NA	353 vaccinees (5.9%), 326 placebo (5.5%)	352 vaccinees (5.9%), 326 placebo (5.5%)
HSIL	1 vaccinees, 2 placebo	NA	43 vaccinees (0.7%), 33 placebo (0.6%)	42 vaccinees (0.7%), 33 placebo (0.6%)
HPV16 (by PCR)	NA	NA	238 vaccinees (8.9%), 227 placebo (8.4%)	543 vaccinees (9.1%), 545 placebo (9.1%)
HPV18 (by PCR)	NA	NA	86 vaccinees (3.2%), 83 placebo (3.1%)	230 vaccinees (3.8%), 242 placebo (4.0%)
Serious adverse event	2 vaccinees (1%), 2 placebo (1%)	NA	45 vaccinees (0.7%), 54 placebo (0.9%)	46 vaccinees (0.7%), 54 placebo (0.9%)
Vaccine related serious adverse event	NA	NA	3 vaccinees, 2 placebo	1 vaccinees, 2 placebo

Table 2 Pooled efficacy of HPV vaccine according to per-protocol analysis*

Study	Vaccine		Placebo		Total	Efficacy	95% CI	
	Total	Cases	Total	Cases			Upper bound	Lower bound
Incident HPV 16 infection								
Harper, 2006	414	1	385	40	799	97.7		
Garland, 2007	1888	0	1847	39	3735	100.0		
FUTURE II study group, 2007	4559	1	4408	35	8967	97.2		
Pooled estimate**					13501	97.8	99.40	92.40
Incident HPV 18 infection								
Harper, 2006	414	2	385	17	799	89.1		
Garland, 2007	2101	0	2120	16	4221	100.0		
FUTURE II study group, 2007	5055	0	4970	11	10025	100.0		
Pooled estimate**					15045	93.4	98.0	78.9
Persistent HPV 16 infection								
Harper, 2006	414	1	385	19	799	95.1		
Villa, 2006	199	1	198	28	397	96.4		
Pooled estimate**					1196	95.5	98.9	81.5
Persistent HPV 18 infection								
Harper, 2006	414	0	385	5	799	100.0		
Villa, 2006	224	1	224	11	448	90.9		
Pooled estimate**					1247	90.8	98.3	51.5
Persistent HPV 16/18 infection								
Harper, 2006	414	1	385	23	799	96.0		
Villa, 2006	235	2	233	45	468	95.6		
Pooled estimate**					1267	95.1	98.5	84.6
CIN2+ associated HPV 16/18								
Villa, 2006 (CIN1+)	235	0	233	3	468	100.0		
Garland, 2007	2241	0	2258	32	4499	100.0		
FUTURE II study group, 2007	5305	1	5260	42	10565	97.6		
Pooled estimate**					15532	97.4	99.4	89.5

*Full 3-dose injection among naive women **** All heterogeneity tests >0.49, Fixed effect models were used

Table 3 Pooled efficacy of HPV vaccine according to intention to treat analysis 1*

Study	Vaccine		Placebo		Total	Efficacy	95% CI	
	Total	Cases	Total	Cases			Upper bound	Lower bound
Incident HPV 16 infection								
Harper, 2006	481	7	470	55	951	87.6		
Garland, 2007	2248	0	2259	53	4507	100.0		
FUTURE II study group, 2007	5054	3	5043	51	10097	94.1		
Pooled estimate**					15555	93.1	96	87.2
Incident HPV 18 infection								
Harper, 2006	481	3	470	29	951	89.9		
Garland, 2007	2253	1	2550	22	4803	94.9		
FUTURE II study group, 2007	5602	0	5602	16	11204	100.0		
Pooled estimate**					16958	93	97.3	81.8
Persistent HPV 16 infection								
Harper, 2006	481	2	470	29	951	93.3		
Villa, 2006	225	3	229	34	454	91.0		
Pooled estimate**					1405	91.3	96.5	78.5
Persistent HPV 18 infection								
Harper, 2006	481	0	470	8	951	100.0		
Villa, 2006	253	1	253	12	506	91.7		
Pooled estimate**					1457	92.5	98.6	60.9
Persistent HPV 16/18 infection								
Harper, 2006	481	2	470	34	951	94.3		
Villa, 2006	256	4	254	58	510	93.2		
Pooled estimate**					1461	92.6	96.7	83.1
CIN2+ associated HPV 16/18								
Harper, 2006	481	0	470	5	951	100.0		
Villa, 2006 (CIN1+)	258	0	256	7	514	100.0		
Garland, 2007	2667	0	2684	43	5351	100.0		
FUTURE II study group, 2007	5865	3	5863	62	11728	95.2		
Pooled estimate**					18544	96.2	98.5	90.1

Study	Vaccine		Placebo		Total	Efficacy	95% CI	
	Total	Cases	Total	Cases			Upper bound	Lower bound
CIN2+ associated HPV anytype								
Harper, 2006	505	3	497	11	1002	73.2	92.3	2.8

*At least one dose injection among naive women

****** All heterogeneity tests >0.10, Fixed effect models were used

Table 4 Pooled efficacy of HPV vaccine according to intention to treat analysis 2*

Study	Vaccine		Placebo		Total	Efficacy	95% CI	
	Total	Cases	Total	Cases			Upper bound	Lower bound
Incident HPV 16 infection								
Garland, 2007	2723	58	2732	106	5455	45.1		
FUTURE II study group, 2007	6087	77	6080	132	12167	41.7		
Pooled estimate**					17622	42.5	53.4	29.2
Incident HPV 18 infection								
Garland, 2007	2723	8	2723	33	5446	75.8		
FUTURE II study group, 2007	6087	6	6080	29	12167	79.3		
Pooled estimate**					17613	77.3	87.3	59.5
CIN2+ associated HPV 16/18								
Garland, 2007	2723	52	2732	80	5455	34.8		
FUTURE II study group, 2007	6087	83	6080	148	12167	44.0		
Pooled estimate**					17622	40.1	51.5	26.1
CIN2+ associated HPV anytype								
Garland, 2007 (CIN1+)	2723	344	2732	421	5455	18.0		
FUTURE II study group, 2007	6087	219	6080	266	12167	17.8		
Pooled estimate**					17622	16.4	24.9	7.1

*At least one dose injection among women regardless status of prior HPV infection

****** All heterogeneity tests >0.50, Fixed effect models were used

Appendix 4

Work package 2.3: The systematic review of the operating characteristics of screening tests including VIA, Pap smear, and HPV DNA testing

Introduction

Precise estimates of screening test accuracy including sensitivity and specificity are important to determine policy decision of screening program. Recommendation for optimal frequency screening, management of mild abnormalities, and use of newer technology depend on the screening test property. Cervical cancer is highly preventable through cytology screening program with Papanicolaou (Pap) smears that facilitate the detection and treatment of pre-cancerous lesions. Alternative methods, such as DNA testing for human papillomavirus (HPV) and simple visual screening with acetic acid (VIA) could be used as an adjunct to cytology to identify women at risk of cervical cancer. Classification for cervical cytology was compared as shown in the following diagram [1].

Figure 1 Map of classification schemes for cervical cytology

<table>
<tr><td>Classification System</td><td colspan="8">Cytology Classification</td></tr>
<tr><td>The Bethesda System</td><td rowspan="5">Normal</td><td colspan="2" rowspan="2">Infection
Reactive Repair</td><td>ASCUS</td><td colspan="4">Squamous Intraepithelial Lesion (SiL)</td><td rowspan="5">Invasive Carcinoma</td></tr>
<tr><td></td><td colspan="2">Low Grade (LSIL)</td><td colspan="3">High Grade (HSIL)</td></tr>
<tr><td>Richart</td><td colspan="3" rowspan="2"></td><td colspan="4">Cervical Intraepithelial Neoplasia (CIN)</td></tr>
<tr><td>Condyloma</td><td>Grade I</td><td>Grade II</td><td colspan="2">Grade III</td></tr>
<tr><td>Reagan (WHO)</td><td colspan="3">Atypia</td><td colspan="2">Mild Dysplasia</td><td>Moderate Dysplasia</td><td>Severe Dysplasia</td><td>In situ Carcinoma</td></tr>
<tr><td>Papanicolaou</td><td>I</td><td colspan="3">II</td><td colspan="3">III</td><td colspan="2">IV</td><td>V</td></tr>
</table>

Abbreviation and the terminology
CIN: Cervical intra-epithelial neoplasia
SIL: Squamous intraepithelial lesion
HSIL: High grade of squamous intraepithelial lesion
LSIL: Low grade of squamous intraepithelial lesion
ASCUS: Atypical squamous cells of undertermined significance
VIA: Visual inspection of the cervix with 3% -5% acetic acid
VIAM: VIA with magnifying device
HPV: Human papilloma virus
HR type: High risk type of HPV of cervical carcinogensis included HPV type 16,18,31,33,35,39,45,51,52,56,58,59, and 68.
HCT or HC1: First generation hybrid capture for HPV detection from cervical sampling
HC2: Second generation assay by hybrid capture for HPV detection from cervical cells specimen.

Objective

The aim of the study was to systematically review the operating characteristics of screening tests including VIA, Pap smear, and HPV DNA testing.

Methods

Searching

The Ovid (Medline) electronic database from January, 1996 to Febuary, 2007 was searched, using the following key search words.
1. MESH term "Uterine Cervical Neoplasms" with subheading "diagnosis"
2. keywords "sensitivity" or "specificity"
3. keyword "pap smear" or "visual inspection with acetic acid" or "HPV DNA testing"

The search strategy was: #1 and #2 and #3, limited to English language. Only journal article type was included. Eighty articles were retrieved. The title and abstract of each citation were screened first, and full report was screened second if necessary to select the relevant articles according to selection criteria. Full-texts of those selected studies were retrieved, reviewed and extracted for relevant data by two independent reviewers.

Inclusion criteria

The study must compare the screening test (either of Pap smear, VIA, or HPV DNA testing) to the reference standard on the same patients or slides as histological confirmation and or Colposcopy. Of eighty studies, there were 32 studies fulfilled this criteria.

Exclusion criteria

1. Some participants in the study were not evaluated for reference standard (histologic confirmation and or colposcpy)
2. No available data for all of true positive, false positive, true negative and false negative, according to criterion validity of the test (four cells of a 2X2 tables).

Eleven studies were excluded [2-12]. Finally, twenty one studies were relevant for this systematic review with 12, 15, and 9 studies relevant for reviewing the operating characteristics of VIA-VIAM, Pap smear, and HPV DNA testing respectively [13-34].

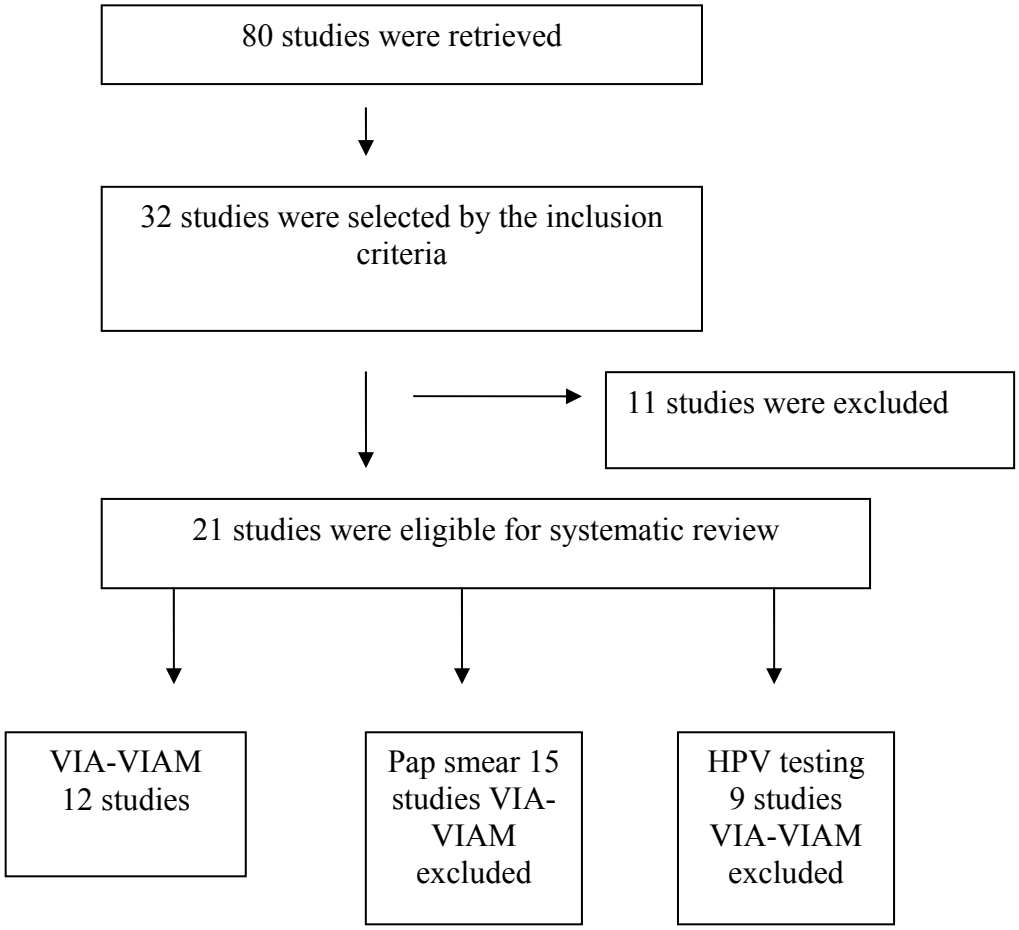


Figure 2 Literature review profile

Threshold of screening tests

1. Pap smear: Cytologic abnormality of Pap smears was defined as HSIL (equivalent category by other classifications) or worse. However, ASCUS or LSIL (or equivalent categories by other classifications) could be used as the threshold if data of HSIL was not available.
2. VIA (including VIAM): Abnormal VIA and VIAM were defined as white plaques, ulcer or cancerous like lesions by naked-eye visual inspection of the cervix after applying 3-5% acetic acid with a cotton swab and by using a magnifying device respectively.
3. HPV testing: A positive HC1 (HCT) test was defined as that with relative light unit (RLU) positive control ratios of 1.0 or greater (equivalence of 10 picrogram/ml). A positive HC2 test was defined as that with relative light unit (RLU) positive control ratios of 1.0 or greater (equivalence of 1 picrogram/ml) in most cases.

Outcome and outcome threshold

Histology or combination of Colposcopy and histology were used as gold standard in this review. Normal colposcopy was defined as normal. Abnormal Colposcopy must have histological confirmation by material obtained by colposcopy-directed biopsy, loop exiscion, or endocervical curettage. Histologic threshold for positive outcome from screening tests was CIN2 or worse (or equivalent categories by other classifications).

Covariate information

Characteristics of study population (place, inclusion and exclusion criteria, age distribution), type of screening test (conventional Pap smear, VIA, and HPV testing), screening setting (primary screening or screening among women with previous cytological abnormality), bias assessment of screening and gold standard (blinding of testing or not) were included. The following study characteristics were summarized systematically in table 1.

Definition of accuracy measures and Statistical analysis

Descriptive statistics of each study was presented. True positive (TP), true negative (TN), false positive (FP), and false negative (FN) of the screening test against the gold standard from each study were extracted to construct 2X2 tables for calculation of sensitivity and specificity, positive predictive value and negative predictive value. A meta-analysis, yielding a quantitative summary measure of each screening test was implemented. Subgroup analysis was reported according to important covariate. The variations in accuracy measures in the individual studies and in the pooled measures were displayed graphically using forest plots. A forest plot is a graph where the confidence interval (CI) for each study is represented by a horizontal line and the point estimate. Random-effects models were used for pooling all parameters in this review because of statistically significant interstudy heterogeneity (when $P<0.1$ for Cochran's Q test) in most cases[35,36]. Meta-analyses were performed using the Stata statistical package version 9.0.

Results

VIA-VIAM

There were 12 studies eligible for systematic review of the screening test of VIA or VIAM testing. True positive, true negative cases, false positive, and false negatives cases including sensitivity, specificity, positive predictive value, and negative predictive value with their standard errors were shown in table 2.

Pap smear

There were 15 studies eligible for systematic review of the screening test of conventional Pap smear. True positive, true negative cases, false positive, and false negatives cases including sensitivity, specificity, positive predictive value, and negative predictive value with their standard errors were shown in table 3. Pooled estimates were presented in table 5. Subgroup analysis according to the country, the setting, and the outcome cutoff of HSIL+ were performed and presented in table 7.

HPV testing

There were 9 studies eligible for systematic review of the screening test of HPV testing as HC1 and HC2 testing. True positive, true negative cases, false positive, and false negatives cases including sensitivity, specificity, positive predictive value, and negative predictive value with their standard errors were shown in table 4. Pooled estimates were presented in table 5. Subgroup analysis according to the type of HPV testing, the country and the setting were performed and presented in table 8.

Pooled estimates

Using random effect method, summarized pooled estimates of sensitivity, specificity, positive predictive value, negative predictive value and their standard errors were presented in table 5. Subgroup analysis according to the screening type, the country, the setting, and the outcome cutoff were performed and presented in table 6, 7, and 8 for the screening test of VIA-VIAM and conventional Pap smear and HPV DNA testing respectively. The forest plots of the sensitivity, specificity, PPV, NPV for the VIA testing were shown in figure 1, 2, 3, and 4 respectively. The forest plots of the sensitivity, specificity, PPV, NPV for the VIA-VIAM test were shown in figure 1, 2, 3, and 4 respectively. The forest plots of the sensitivity, specificity, PPV, NPV for the conventional Pap smear were shown in figure 5, 6, 7, and 8 respectively. The forest plots of the sensitivity, specificity, PPV, NPV for the HPV DNA testing were shown in figure 9, 10, 11, and 12 respectively.

Discussion

In this meta-analysis, the accuracy of 3 screening methods: VIA-VIAM, conventional Pap smear, and HPV DNA testing were evaluated. Selection bias was minimized as study characteristics of the excluded studies were comparable to all eligible studies. The study characteristics of the excluded studies were shown and were compared in table 9 and 10 respectively. Predictive values depend on the local disease prevalence, and therefore generalizability of the results is limited.

The highest sensitivity (85.9%, SE=2.9%) was noted in HPV testing, especially in HC2 and in the setting of women who had previously abnormal cytology. The lowest sensitivity (55.2%, SE=7.0%) was noted in conventional Pap smear, especially in developing country or in the primary screening setting. In contrast, the highest specificity (91.5%, SE=1.3%) was noted in conventional Pap smear, especially in the primary screening setting. The lowest specificity (59.7%, SE=4.3%) was found in HPV testing.

VIA-VIAM method has been used widely among developing countries because of easy to perform and therapy in positive result women can be done immediately in the same visit. The accuracy of the VIA-VIAM are low with the sensitivity and specificity of 71.6% (SE=2.5%) and 79.3% (SE=1.1%) respectively. However, its negative predictive value is high (98.7%, SE=0.2%) comparable to those of other screening tests. Almost all studies undertaken VIA-VIAM in this meta-analysis were in developing countries with primary screening setting.

Table 1 Characteristics of the studies (21 studies)

Author-Year	Country	Population		Age (years)	Screening test			Blinding
		Characteristics	Exclusion criteria		VIA or VIAM (13)*	Pap smears (15)*	HPV testing (9)*	
University of Zimbabwe,1999	Zimbabwe	Primary care setting	pregnant, previous history of cervical cancer or hysterectomy	25-55	yes	yes	-	yes
Singh, 2001	India	Women with gynecological symptoms	not mentioned	mean = 37.1	yes	yes	-	not mentioned
Basu, 2003	Eastern India	Primary care setting	poor general health, pregnant women, prior hysterectomy or treatment for cervical precancers or cancer	30-64	yes	yes	-	yes
Winkler, 2003	USA	Women with prior abnormal pap smear	not mentioned	18–50	yes	-	-	yes
Bhatla, 2004	India	Women with gynecological symptoms	prior hysterectomy, unmarried, pregnancy, and obvious growth on cervix	30-74	yes	-	-	yes
Sankaranarayanan, 2004	India	Primary care setting	pregnant, history of cervical cancer or hysterectomy	25-65	yes	-	-	yes

Author-Year	Country	Population		Age (years)	Screening test			Blinding
		Characteristics	Exclusion criteria		VIA or VIAM (13)*	Pap smears (15)*	HPV testing (9)*	
Sankaranarayanan, 2004	India and Africa	Primary care setting	pregnant and had previous history of cervical cancer or hysterectomy	25-65	yes	-	-	yes
De Vuyst, 2005	Kenya	Primary care setting	pregnancy	25—55	yes	yes	yes	yes
Doh, 2005	Cameroon	Primary care setting	previous history of cervical cancer, total hysterectomy or cervical amputation	30-60	yes	yes	-	yes
Goel, 2005	India	Screening setting	nulliparous, pregnant, active vaginal bleeding, frank growth on the cervix	30-34	yes	yes	-	yes
Shastri, 2005	India	Primary care setting	past history of cervical neoplasia	30–65	yes	yes	yes	yes
Sangwa-Lugoma, 2006	Congo	Primary care setting	not pregnant, no intact uterus	30 up	yes	yes	-	yes
Hall, 1996	USA	Women with ASCUS or LSIL	pregnant	mean ages = 24.1	-	yes	yes	yes
Witt, 2003	Austria	Screening setting	not mentioned	10–79	-	yes	yes	not mentioned

Author-Year	Country	Population		Age (years)	Screening test			Blinding
		Characteristics	Exclusion criteria		VIA or VIAM (13)*	Pap smears (15)*	HPV testing (9)*	
Singer, 2003	UK and Australia	Primary care setting	current menstrual period, pregnancy, total hysterectomy, and surgical treatment to the cervix within the previous 3 months.	18 up	-	yes	-	Yes
Sarian, 2004	Italy, Brazil	Women with CIN2+ confirmed in the Ccnization specimens	pregnancy, immunosuppresion, positive HIV testing	20-60	-	yes	yes	Yes
Lee, 2004	Korea	Women with ASCUS+	recent surgical treatment for their cytological abnormalities	14-88	-	yes	yes	not mentioned
Boonlikit, 2005	Thailand	Primary care setting	history of cervical cancer or know case of CIN, pregnancy, previous cervical operation or total hysterectomy, cervical abnormality, radiotherapy	18 - 69	-	yes	-	yes
Monsoneco, 2006	France	Women with ASCUS, LSIL, HSIL and normal pap smear but who had previous or current HPV related disease	immunosuppressed, pregnant	16-70	-	yes	yes	yes

Author-Year	Country	Population		Age (years)	Screening test			Blinding
		Characteristics	Exclusion criteria		VIA or VIAM (13)*	Pap smears (15)*	HPV testing (9)*	
Ferris, 1998	USA	Women with previous pap smear of ASUCUS or LSIL	current pregnancy, immunosuppression, cervical cancer within the past year, previous colposcopy or treatment of cervical neoplasia within the past	18 up	-	-	yes	yes
Kuhn, 2000	South Africa	Primary care setting	not mentioned	35-65	-	-	yes	Yes

Table 2 Operating characteristics of VIA-VIAM (12 studies)

Study	Author-Year	Gold Standard	Screening test	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity	Specificity	PPV	NPV	Prevalence
1	**University of Zimbabwe, 1999**	Colposcopy, with biopsy as indicated	VIA	HSIL+	158	1233	691	48	2130	76.7	64.1	18.6	96.3	9.7
2	**Singh, 2001**	Colposcopy, with biopsy as indicated	VIA	Moderate dysplasia+	118	218	49	17	402	87.4	81.6	70.7	92.8	33.6
3	**Basu, 2003**	Colposcopy, with biopsy as indicated	VIA	CIN 2+	68	4697	1024	54	5843	55.7	82.1	6.2	98.9	2.1
4	**Basu, 2004**	Colposcopy, with biopsy as indicated	VIAM	CIN 2+	74	4761	959	48	5842	60.7	83.2	7.2	99.0	2.1
5	**Winkler, 2003**	Colposcopy, with biopsy as indicated	VIAM	CIN 2+	24	60	27	16	127	60.0	69.0	47.1	78.9	31.5
6	**Bhatla, 2004**	Colposcopy, with biopsy as indicated	VIA	HSIL+	7	58	34	1	100	87.5	63.0	17.1	98.3	8.0
7	**Sankaranarayanan, 2004**	Colposcopy, with biopsy as indicated	VIA	HSIL+	194	14416	2187	103	16900	65.3	86.8	8.1	99.3	1.8
8	**Sankaranarayanan, 2004**	Colposcopy, with biopsy as indicated	VIAM	HSIL+	202	14406	2197	95	16900	68.0	86.8	8.4	99.3	1.8
9	**Sankaranarayanan, 2004**	Colposcopy, with biopsy as indicated	VIA	HSIL+	1056	45857	7792	276	54981	79.3	85.5	11.9	99.4	2.4

Study	Author-Year	Gold Standard	Screening test	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity	Specificity	PPV	NPV	Prevalence
10	**De Vuyst, 2005**	Colposcopy, with biopsy as indicated	VIA	CIN II+	44	460	133	16	653	73.3	77.6	24.9	96.6	9.2
11	**Doh, 2005**	Biopsy	VIA	LSIL+	245	1083	312	103	1743	70.4	77.6	44.0	91.3	20.0
12	**Goel, 2005**	Biopsy	VIA	moderate dysplasia+	12	349	38	1	400	92.3	90.2	24.0	99.7	3.3
13	**Shastri, 2005**	Colposcopy, with biopsy as indicated	VIA	HSIL+	54	3470	454	31	4009	63.5	88.4	10.6	99.1	2.1
14	**Shastri, 2005**	Colposcopy, with biopsy as indicated	VIAM	HSIL+	57	3387	463	28	3935	67.1	88.0	11.0	99.2	2.2
15	**Sangwa-Lugoma, 2006**	Colposcopy, with biopsy as indicated	VIA	CIN 2+	22	221	306	7	556	75.9	41.9	6.7	96.9	5.2

VIA= Visual inspection with Acetic acid, VIAM= Visual inspection with Acetic acid and Magnifier
TP= true positve, TN= true negative, FP= false positive, FN= false negative
PPV=positive predictive value, NPV=negative predictive value

Table 3 Operating characteristics of Pap smear (15 studies)

Study	Author-Year	Gold Standard	Cutoff	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity	Specificity	PPV	NPV	Prevalence
1	**Hall, 1996**	Biopsy and endocervical currettage if normal colposcopy	HSIL	HSIL	9	123	2	17	151	34.6	98.4	81.8	87.9	17.2
2	**University of Zimbabwe, 1999**	Colposcopy, with biopsy as indicated	HSIL+	HSIL+	89	1713	178	112	2092	44.3	90.6	33.3	93.9	9.6
3	**Singh, 2001**	Colposcopy, with biopsy as indicated	Anormal ctology	Moderate dysplasia+	110	210	57	25	402	81.5	78.7	65.9	89.4	33.6
4	**Witt, 2003**	Biopsy	HSIL+	CIN2+	109	105	6	60	280	64.5	94.6	94.8	63.6	60.4
5	**Basu, 2003**	Colposcopy, with biopsy as indicated	Dysplasia	CIN2+	33	4595	383	79	5090	29.5	92.3	7.9	98.3	2.2
6	**Singer, 2003**	Colposcopy, with biopsy as indicated	ASC-H+	CIN2-3	50	541	26	34	651	59.5	95.4	65.8	94.1	12.9
7	**Lee, 2004**	Colposcopy, with cervical biopsy and endocervical curettage as	ASCUS+	CIN2+	151	260	135	47	593	76.3	65.8	52.8	84.7	33.4

Study	Author-Year	Gold Standard	Cutoff	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity	Specificity	PPV	NPV	Prevalence
		indicated												
8	**Sarian, 2004**	Colposcopy, with biopsy as indicated	ASC+	CIN2+	7	66	15	0	88	100.0	81.5	31.8	100.0	8.0
9	**De Vuyst, 2005**	Colposcopy, with biopsy as indicated	HSIL+	CIN2+	43	568	25	17	653	71.7	95.8	63.2	97.1	9.2
10	**Goel, 2005**	Biopsy	Mderate dysplasia+	Mderate dysplasia+	9	48	2	4	63	69.2	96.0	81.8	92.3	20.6
11	**Shastri, 2005**	Colposcopy, with biopsy as indicated	LSIL+	LSIL+	58	3524	43	124	3749	31.9	98.8	57.4	96.6	4.9
12	**Boonlikit, 2005**	Colposcopy, with biopsy as indicated	ASCUS, CIN1+	ASC, CIN1+	1	236	6	14	257	6.7	97.5	14.3	94.4	5.8
13	**Doh, 2005**	Biopsy	LSIL+	LSIL+	166	1314	182	81	1743	67.2	87.8	47.7	94.2	14.2
14	**Sangwa-Lugoma, 2006**	Colposcopy, with biopsy as indicated	HSIL+	CIN2+	13	489	9	15	526	46.4	98.2	59.1	97.0	5.3
15	**Monsonego, 2006**	Biopsy	HSIL+	CIN2+	85	173	15	116	389	42.3	92.0	85.0	59.9	51.7

Table 4 Operating characteristics of HPV testing (9 studies)

Study	Author-Year	Gold Standard	Screening test	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity	Specificity	PPV	NPV	Prevalence
1	**Hall, 1996**	Biopsy and endocervical currettage if normal colposcopy	HCT (Brush sample), HR, cutoff at 1:1	HSIL	14	19	42	1	76	93.3	31.1	25.0	95.0	19.7
2	**Hall, 1996**	Biopsy and endocervical currettage if normal colposcopy	HCT (Lavage sample) , HR, cutoff at 1:1	HSIL	6	29	36	5	76	54.5	44.6	14.3	85.3	14.5
3	**Ferris, 1998**	Colposcopy, with cervical biopsy and endocervical curettage as indicated	HCT, HR, cutoff at 10 pg/ml	CIN 2-3	13	126	95	8	242	61.9	57.0	12.0	94.0	8.7
4	**Ferris, 1998**	Colposcopy, with cervical biopsy and endocervical curettage as indicated	HC II, HR, cutoff at 0.2 pg/ml	CIN 2-3	19	65	156	2	242	90.5	29.4	10.9	97.0	8.7
5	**Kuhn, 2000**	Colposcopy, with cervical biopsy and endocervical curettage as indicated	HC1, HR, cutoff at 10pg/ml	HSIL+	43	2648	127	43	2861	50.0	95.4	25.3	98.4	3.0

Study	Author-Year	Gold Standard	Screening test	Outcome (cutoff)	TP	TN	FP	FN	Total	Sensitivity	Specificity	PPV	NPV	Prevalence
6	**Kuhn, 2000**	Colposcopy, with cervical biopsy and endocervical curettage as indicated	HC2, HR, cutoff at 1pg/ml	HSIL+	76	227	111	10	424	88.4	67.2	40.6	95.8	20.3
7	**Witt, 2003**	Biopsy	HC2, HR, cutoff at 0.23 pg/ml	CIN2+	155	39	72	14	280	91.7	35.1	68.3	73.6	60.4
8	**Lee, 2004**	Colposcopy, with cervical biopsy and endocervical curettage as indicated	HC2, cutoff at1 pg/ml	CIN2+	183	207	188	15	593	92.4	52.4	49.3	93.2	33.4
9	**Sarian, 2004**	Colposcopy, with biopsy as indicated	HC2, HR, cutoff at1 pg/ml	CIN2+	7	70	11	0	88	100.0	86.4	38.9	100.0	8.0
10	**De Vuyst, 2005**	Colposcopy, with biopsy as indicated	HPV testing, HR	CIN2+	51	275	142	2	470	96.2	65.9	26.4	99.3	11.3
11	**De Vuyst, 2005**	Colposcopy, with biopsy as indicated	HPV testing, any types	CIN2+	52	258	204	2	516	96.3	55.8	20.3	99.2	10.5
12	**Shastri, 2005**	Colposcopy, with biopsy as indicated	HC2, HR, cutoff at1 pg/ml	HSIL+	45	3250	226	25	3546	64.3	93.5	16.6	99.2	2.0
13	**Monsonego, 2006**	Biopsy	HC2, HR, cutoff at 1 pg/ml	CIN2+	180	102	86	21	389	89.6	54.3	67.7	82.9	51.7

HR: high risk type of HPV virus

Table 5 Pooled effect of operating characteristics of the screening tests

Screening type	Number of study	Sensitivity	SE	Specificity	SE	PPV	SE	NPV	SE
Pap smear	15	55.2	7.02	91.5	1.33	56.2	9.67	91.8	0.92
HPV testing	9	85.9	2.91	59.7	4.29	31.9	5.97	97.9	0.46
VIA or VIAM	12	71.6	2.47	79.3	1.12	19.2	1.89	98.7	0.15

SE: standard error of the parameter
Random effect model were used for the estimations

Table 6 Subgroup analysis, pooled effect of operating characteristics of VIA-VIAM method

Subgroup	Number of study	Sensitivity	SE	Specificity	SE	PPV	SE	NPV	SE
VIA	11	74.2	2.83	77.2	1.63	21.3	2.58	98.2	0.23
VIAM	4	65.8	2.02	85	1.33	11.3	1.99	99.1	0.23

SE: standard error of the parameter
Random effect model were used for the estimations

Table 7 Subgroup analysis, pooled effect of operating characteristics of Pap smear method

Subgroup	Number of study	Sensitivity	SE	Specificity	SE	PPV	SE	NPV	SE
Outcome cutoff									
HSIL+	12	60.2	7.55	90.7	1.51	60.1	11.84	90.4	1.17
Country									
Developed	5	56.4	7.55	89.4	4.16	75.9	9.9	78.3	6.45
Developing	9	49.6	8.06	93.1	1.56	47.7	9.54	95.4	0.74
Setting									
Primary setting	10	48.7	6.3	94.7	1.35	52.6	12.91	94.4	0.84
Abnormal cytology	4	63.9	14.85	84.6	7.53	63.1	14.31	83.2	8.29

SE: standard error of the parameter
Random effect model were used for the estimations

Table 8 Subgroup analysis, pooled effect of operating characteristics of HPV testing

Subgroup	Number of study	Sensitivity	SE	Specificity	SE	PPV	SE	NPV	SE
Type									
HC1	**6**	**77.7**	**7.76**	**58.7**	**11**	**20.6**	**2.55**	**98.5**	**0.54**
HC2	7	89.4	2.83	59.8	11.2	41.8	9.72	97.2	0.71
Country									
Developed	9	82.7	3.67	52	10.87	34.9	8.19	92.8	1.66
Developing	4	91	4.54	75.4	10.71	21.8	2.91	99.5	0.26
Setting									
Primary setting	6	82.2	5.41	70	4.23	32.9	7.81	98.6	0.46
Abnormal cytology	7	89.9	3.24	50.9	6.96	31.1	9.95	93.4	2.27

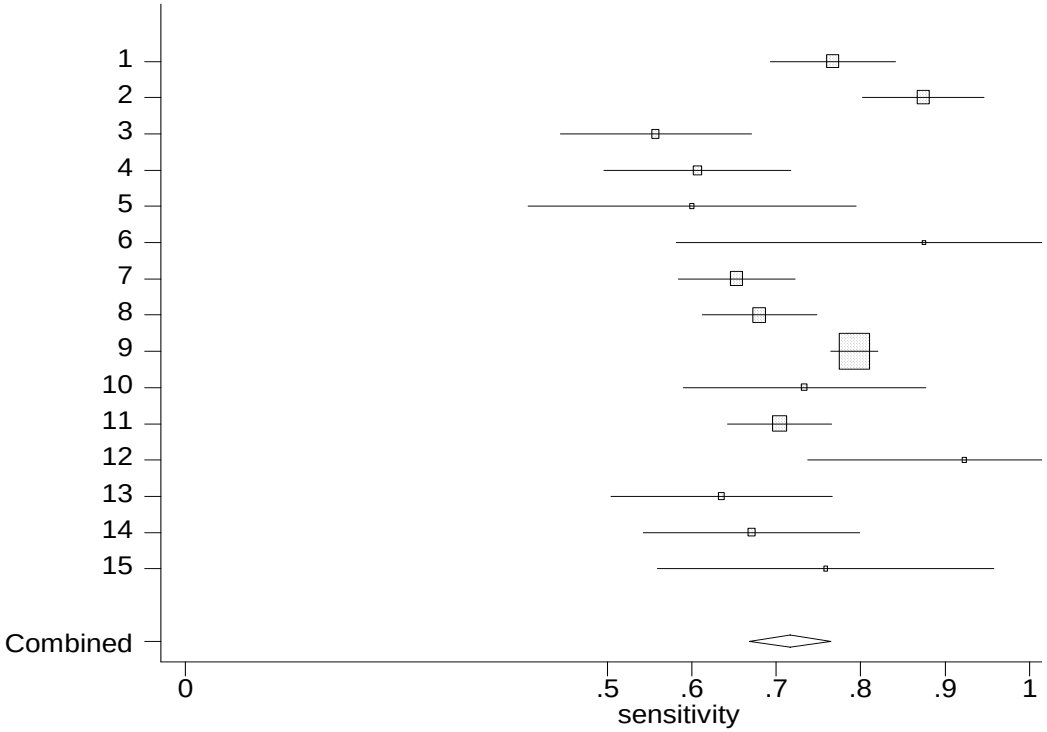
Table 9 Characteristics of the excluded studies

Author-Year	Country	Screening test		
		VIA or VIAM (8)	Pap smears (6)	HPV testing (5)
Ratnam,2000	Canada	-	yes	yes
Blumenthal, 2001	USA	yes	yes	yes
Ngelangel, 2003	Philippines	yes	yes	-
Salmeron, 2003	Mexico	-	yes	yes
Levi, 2003	USA	-	-	yes
Sankaranarayanan, 2003	India	yes	-	yes
Ghaemmaghami, 2004	Iran	yes	yes	-
Bomfirm, 2005	Brazil	yes	yes	-
Sarian, 2005	Latin American	yes	-	-
Elit, 2006	Mongolia	yes	-	-
Escobar,2006	USA	yes	-	-

Table 10 Comparison of study characteristics between eligible and excluded studied

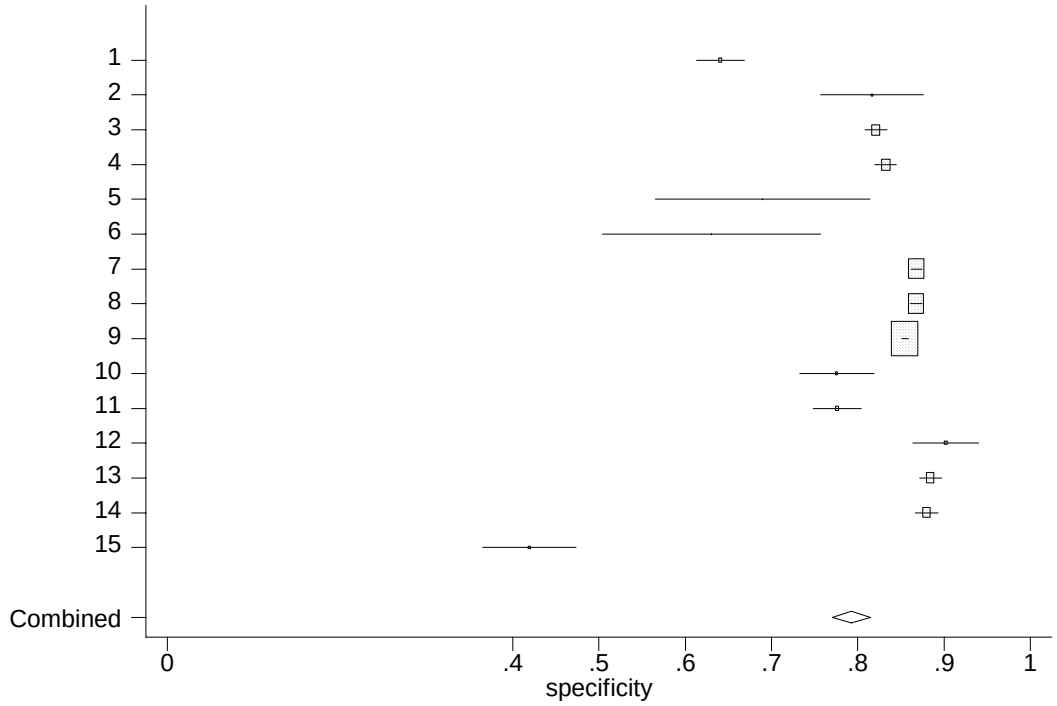
	Eligible studies	%	Excluded studies	%
Country	21		11	
Developing	13	62	7	64
Developed	9	43	4	36
VIA-VIAM	12		8	
Developing	11	92	6	75
Developed	1	8	2	25
Pap smear	15		6	
Developing	10	48	4	67
Developed	6	29	2	33
HPV testing	9		5	
Developing	4	44	2	40
Developed	5	56	3	60

Figure 1 Forest plot of the sensitivity of VIA-VIAM method



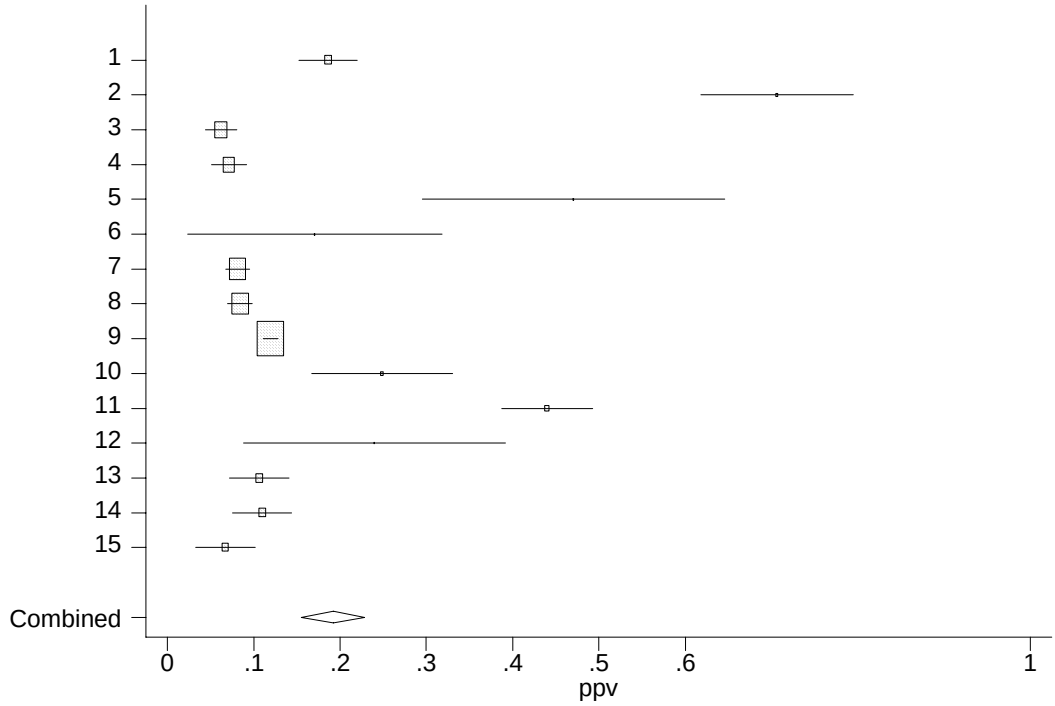
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 2 Forest plot of the specificity of VIA-VIAM method



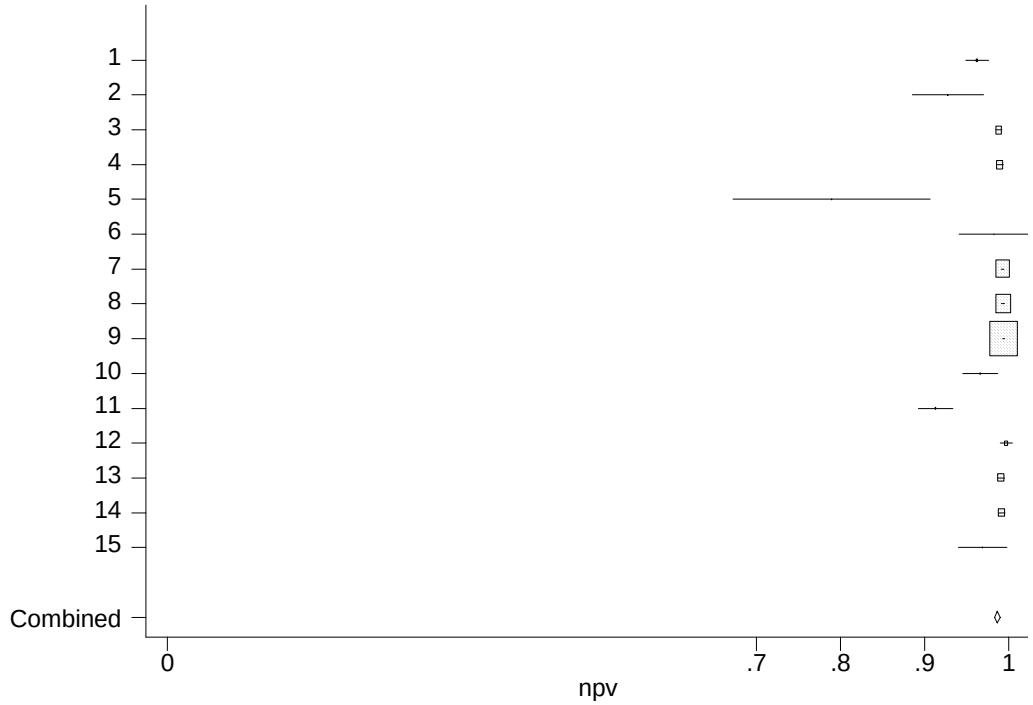
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 3 Forest plot of the positive predictive value of VIA-VIAM method



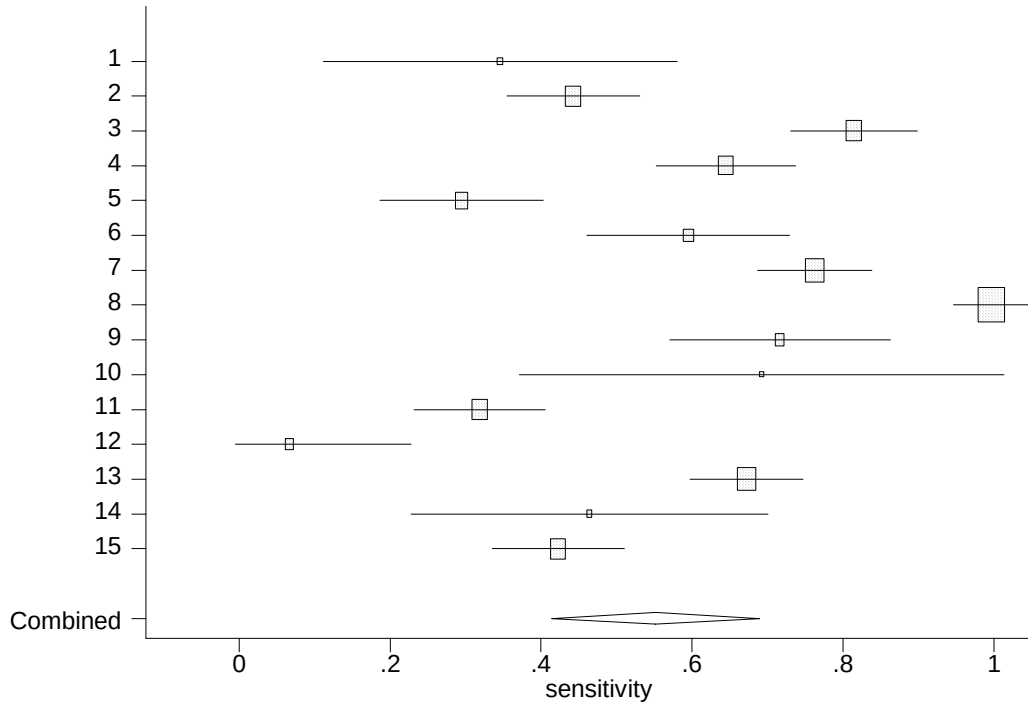
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 4 Forest plot of the negative predictive value of VIA-VIAM method



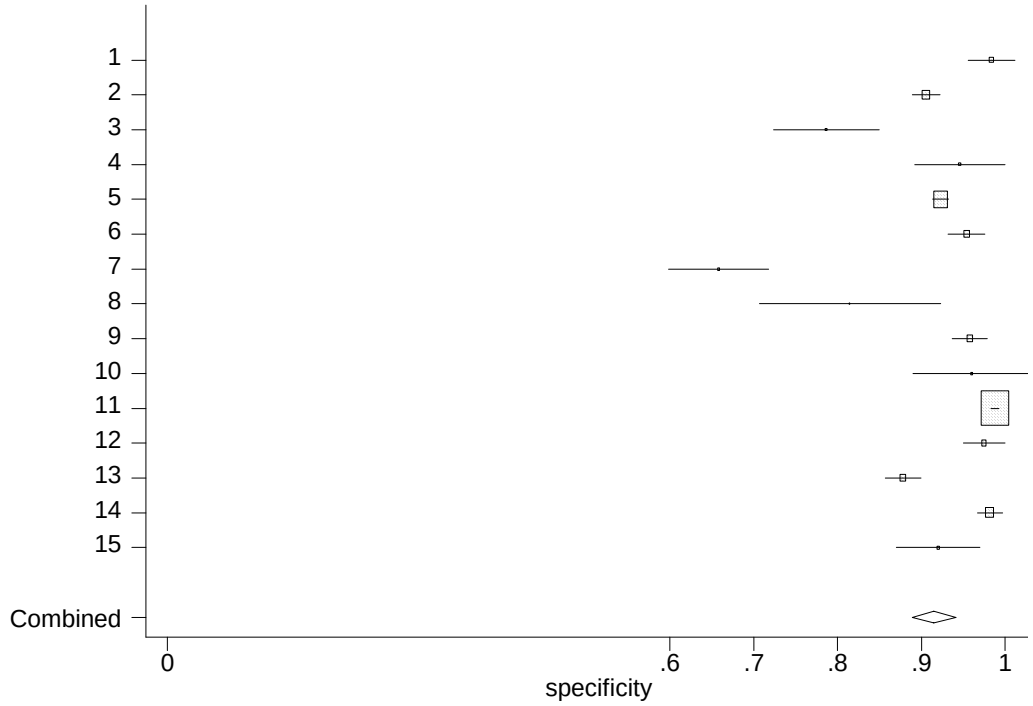
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 5 Forest plot of the sensitivity of Pap smear method



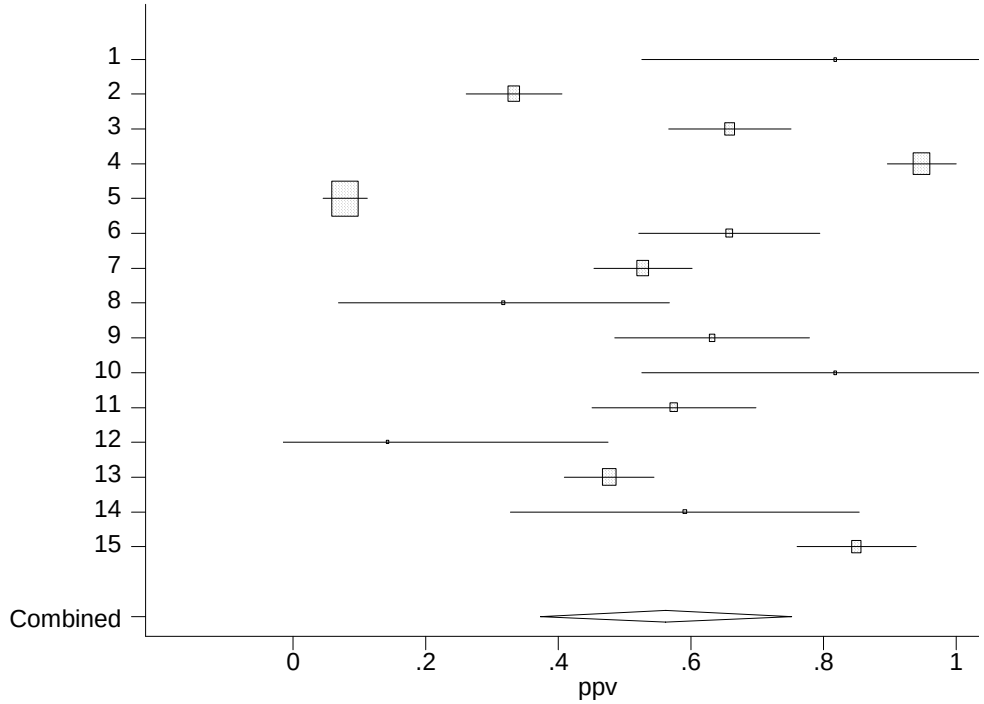
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 6 Forest plot of the specificity of Pap smear method



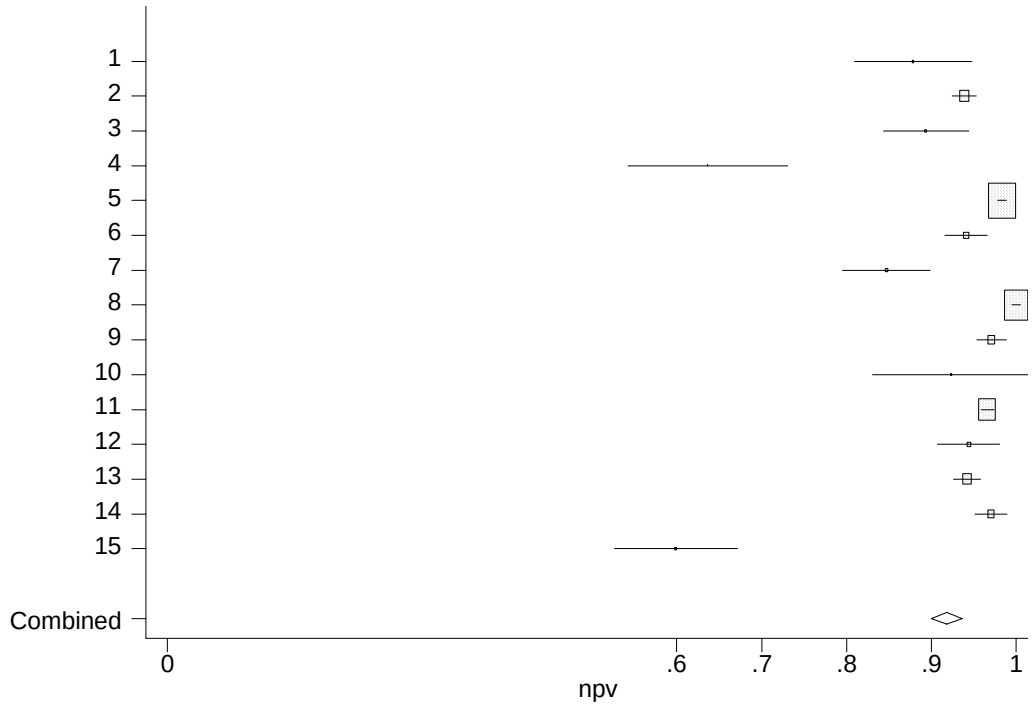
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 7 Forest plot of the positive predictive value of Pap smear method



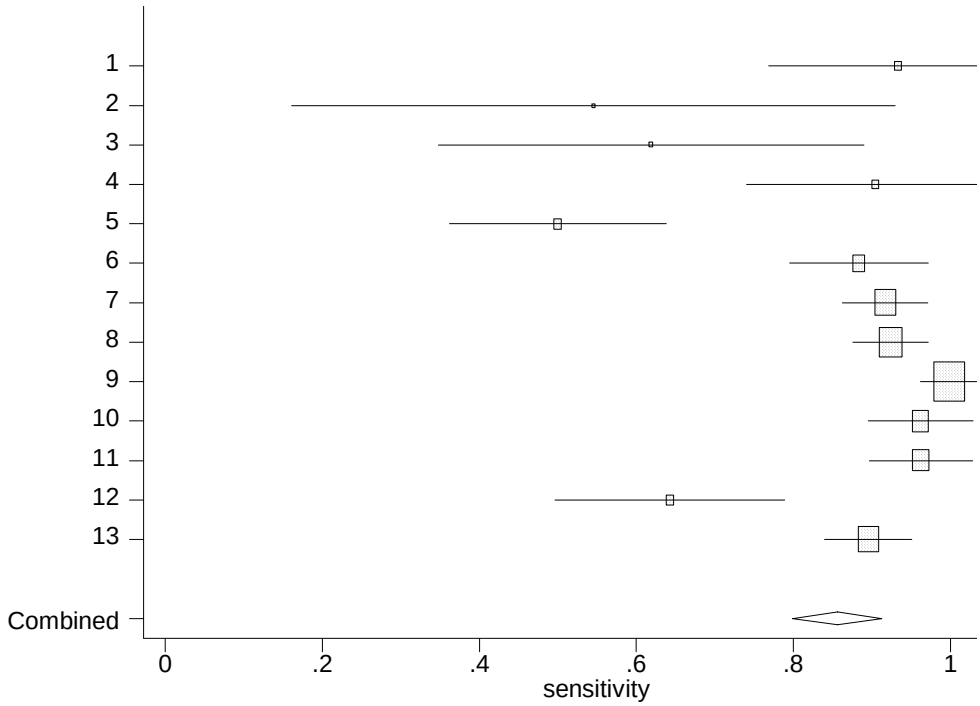
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 8 Forest plot of the negative predictive value of Pap smear method



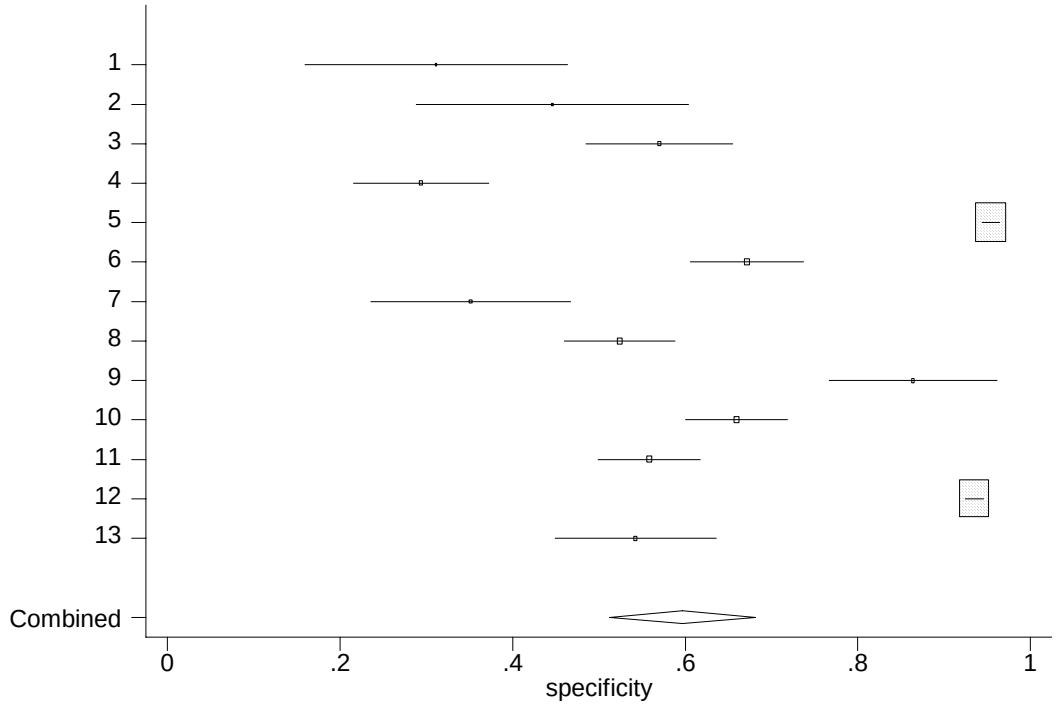
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 9 Forest plot of the sensitivity of HPV testing method



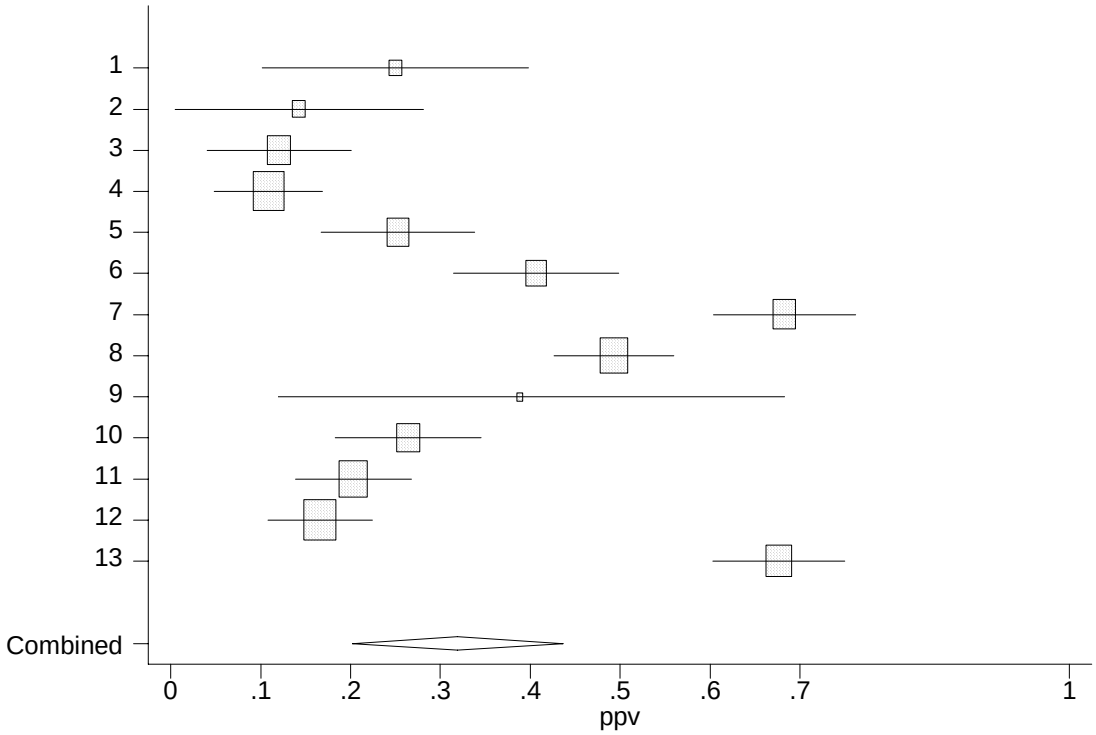
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 10 Forest plot of the specificity of HPV testing method



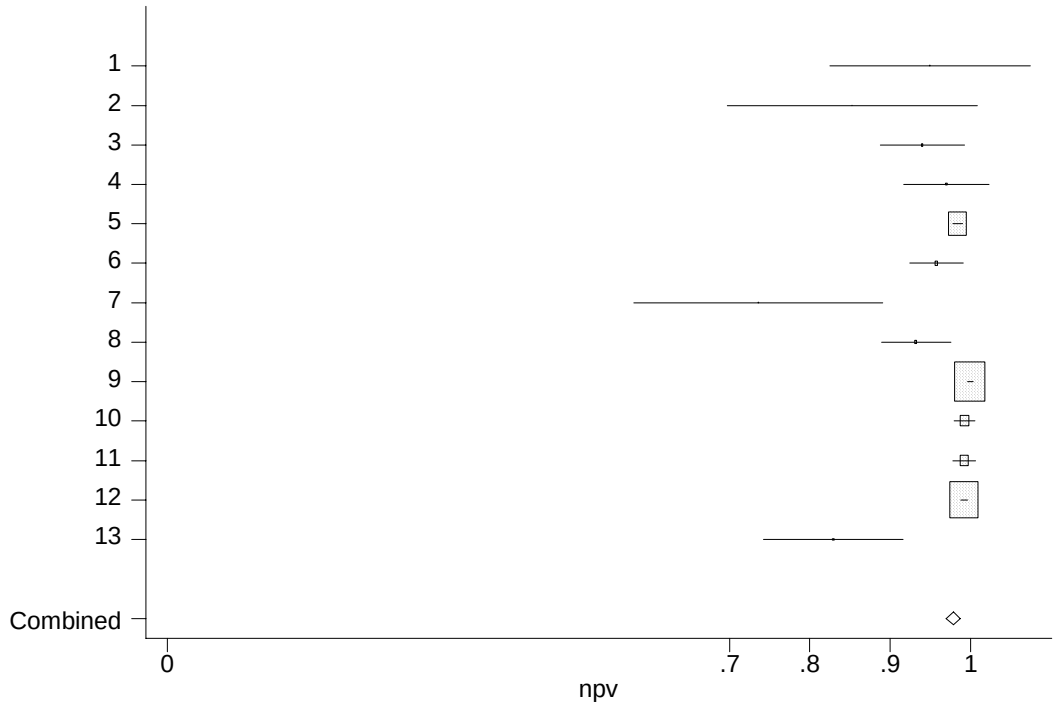
The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 11 Forest plot of the positive predictive value of HPV testing method



The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

Figure 12 Forest plot of the negative predictive value of HPV testing method



The value of the plotted parameter is represented by a rectangular, the surface of which is proportional to the weight that the study contributes to the meta-analysis. The width of the horizontal line depicts the 95% confidence interval. The 95% confidence interval of the pooled estimate is displayed at the bottom as a diamond.

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