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Ρηγοπούλου Ειρήνη

Διπλωματική Εργασία υποβληθείσα στο Τμήμα Οικονομικής Επιστήμης

του Πανεπιστημίου Πειραιώς για την απόκτηση

Μεταπτυχιακού Διπλώματος Ειδίκευσης στα Οικονομικά και Διοίκηση της Υγείας.

Πειραιάς, 2019

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Διπλωματική Εργασία υποβληθείσα στο Τμήμα Οικονομικής Επιστήμης του Πανεπιστημίου Πειραιώς για την απόκτηση Μεταπτυχιακού Διπλώματος Ειδίκευσης στα Οικονομικά και Διοίκηση της Υγείας

Πειραιάς, 2019

UNIVERSITY of PIRAEUS

DEPARTMENT of ECONOMICS

M.Sc. in Health Economics and Management

A Systematic review of the cost-effectiveness of the vaccination against HPV

Rigopoulou Eirini

Master Thesis submitted to the Department of Economics
of the University of Piraeus in partial fulfillment of the requirements
for the degree of M.Sc. in Health Economics and Management

Piraeus, Greece, 2019

Στον σύζυγό μου Παναγιώτη και στην κόρη μας Εμμέλεια

Ευχαριστίες

Θα ήθελα να ευχαριστήσω τον Αναπληρωτή Καθηγητή, κύριο Βοζίκη Αθανάσιο για την καθοδήγηση του στην εκπόνηση της παρούσας εργασίας, για τις πολύτιμες συμβουλές του καθώς και για την εξαιρετική συνεργασία μας.

Ευχαριστώ επίσης τους γονείς μου, Κωνσταντίνο και Διονυσία Ρηγοπούλου καθώς και τον αδερφό μου Παναγιώτη για την συνεχή στήριξη τους.

Πάνω απ'όλους θα ήθελα να ευχαριστήσω τον σύζυγό μου, Παναγιώτη Σαμαρτζή για την απεριόριστη υπομονή, κατανόηση, στήριξη και βοήθεια που μου προσφέρει εδώ και πολλά χρόνια.

Μία συστηματική ανασκόπηση της βιβλιογραφίας σε μελέτες κόστους – αποτελεσματικότητας του εμβολιασμού ενάντια στον HPV

Σημαντικοί όροι: κόστος – αποτελεσματικότητα, οικονομική αξιόλογηση, ICER, HPV, εμβόλιο, ιός ανθρωπίνων θηλωμάτων

Περίληψη

Υπόβαθρο: Ο HPV (Ιός των ανθρωπίνων θηλωμάτων) είναι ένας ιός που υπάρχει στο DNA και μολύνει το δέρμα και τις βλεννογόνους κοιλότητες των ανθρώπων και είναι σε πολλές περιπτώσεις υπεύθυνος στην εμφάνιση καρκινικών ή προκαρκινικών αλλοιώσεων σε πολλά σημεία του σώματος. Τα τελευταία χρόνια σε προσπάθεια αντιμετώπισης του ιού έχουν ενταχθεί εμβόλια στο πλαίσιο των εθνικών εμβολιασμών των περισσοτέρων κρατών. Υπάρχουν 3 είδη εμβολίων: Το διδύναμο που στοχεύει στους τύπους 16 και 18 του ιού ώστε να αποτρέψει τον καρκίνο του τραχήλου της μήτρας. Το τετραδύναμο το οποίο στοχεύει στους τύπους 6, 11, 16 και 18 ώστε να αποτρέψει τα κονδυλώματα και αποτρέψει τον καρκίνο του τραχήλου της μήτρας. Το εννιαδύναμο που στοχεύει στους τύπους 6, 11, 16, 18, 31, 33, 45, 52, και 58 του ιού και προστατεύει από τον καρκίνο του τραχήλου της μήτρας, τα κονδυλώματα καθώς και από καρκίνους του πρωκτού, του κόλπου, και του αιδοίου.

Μεθοδολογία: Τα τελευταία χρόνια πολλές μελέτες έχουν διεξαχθεί με σκοπό να προσδιορίσουν το κόστος και την αποτελεσματικότητα των εμβολίων έναντι του ιού των ανθρωπίνων θηλωμάτων. Σκοπός της παρούσας εργασίας είναι να συγκεντρώσει και να αναλύσει όλα τα διαθέσιμα δεδομένα από μελέτες που έχουν γίνει τα τελευταία έτη αναφορικά με αναλύσεις κόστους – αποτελεσματικότητας των εμβολίων έναντι του HPV. Επίσης, να βρει συσχετίσεις μεταξύ διαφόρων μεταβλητών που υπάρχουν συχνά στις μελέτες αυτές, καθώς και να εντοπίσει σε ποιους παράγοντες δίνεται έμφαση κατά της διεξαγωγή τέτοιων μελετών. Μία συστηματική ανασκόπηση της βιβλιογραφίας πραγματοποιήθηκε μέσω της βάσης Pubmed καθώς και της Cochrane Library χρησιμοποιώντας σχετικές λέξεις-κλειδιά. Συγκεκριμένα κριτήρια εισαγωγής καθόρισαν ποιες μελέτες συμπεριλήφθηκαν σε αυτή την συστηματική ανασκόπηση και ποιες όχι.

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Αποτελέσματα: Η αναζήτηση στη βιβλιογραφία απέδωσε 264 μελέτες για περαιτέρω αξιολόγηση. 235 από αυτές αποκλείστηκαν είτε γιατί δεν αποτελούσαν οικονομική αξιολόγηση, είτε γιατί ήταν ήδη κάποια ανασκόπηση, είτε είχαν μελετηθεί τα εμβόλια από κάποια άλλη σκοπιά μη σχετική με το εξεταζόμενο θέμα**.** Συνολικά 29 μελέτες συμπεριλήφθηκαν σε αυτή την ανασκόπηση. Το 12% έδειξαν ότι το εμβόλιο έχει θετικό αποτέλεσμα στις αναλύσεις κόστους – αποτελεσματικότητας ενώ το 88% των μελετών όχι. Επίσης κάποιες από τις μελετώμενες μεταβλητές έχουν θετική ή αρνητική επιρροή στις αναλύσεις των μελετών.

Συμπεράσματα: Η σύγκριση διαφορετικών μελετών οι οποίες χρησιμοποιούν διαφορετικά μοντέλα δεν μπορεί να οδηγήσει σε ντετερμινιστικά αποτελέσματα. Το εμβόλιο γενικά θα πρέπει να θεωρείται αποτελεσματικό με βάση το κόστος του κάτω από συγκεκριμένες προϋποθέσεις. Τα επιπλέον κόστη που προκύπτουν από τον εμβολιασμό του στοχευμένου πληθυσμού ισοσταθμίζονται με αυτά που θα υπήρχαν αν αντιμετωπίζονταν οι ασθένειες. Ωστόσο, τα αποτελέσματα πρέπει να ερμηνευτούν με ιδιαίτερη προσοχή. πρέπει να λάβουν υπ'όψιν τους τα αποτελέσματα καθώς και να σκεφτούν να αναθεωρήσουν την τιμή του εμβολίου μιας και είναι πιθανότητα ο παράγοντας που επιδρά περισσότερο στο κόστος και την αποτελεσματικότητα.

A Systematic review of the cost-effectiveness of the vaccination against HPV

Keywords: cost – effectiveness, economic evaluation, ICER, HPV, vaccine, Human papilloma virus

Abstract

Background: HPV (Human Papillomavirus) is a DNA virus that infects the skin and mucous membranes of humans and is in many cases responsible for the appearance of cancerous or precancerous lesions in many parts of the body. In recent years, vaccines have been integrated into national vaccines in most countries in an effort to combat the virus. There are 3 types of vaccines: Bivalent vaccine targets on HPV types 16, 18 to prevent cervical cancer. Quadrivalent vaccine targets on HPV type 6, 11, 16, 18 to prevent genital warts and cervical cancer. Ninevalent targets on types 6, 11, 16, 18, 31, 33, 45, 52, and 58 which protects from cervical cancer and genital warts too but also anal, vaginal, and vulvar cancer.

Methodology: In the recent years many studies have been conducted in order to determine the cost – effectiveness of the vaccines against HPV. The purpose of this work is to collect and analyze all available data from these studies. Another purpose is to find correlations between the various variables that are often present in these studies and identify which factors are more relevant when conducting such studies. A systematic review of the literature was performed through Pubmed and Cochrane Library by using relevant keywords. Specific Inclusion and Exclusion criteria set the boundaries for this systematic review.

Results: The search engine identified 264 studies retrieved for evaluation. 235 of those studies were excluded either because their focus was not economic evaluation, or they were already reviews, or they were editorials of HPV vaccination strategies not of interest. A of total 29 studies were included in the review. 12% of them showed that the vaccine is not cost effective and 88% showed that the vaccine is cost effective. Also some of the studied variables have negative or positive effect on the cost – effectiveness analysis.

Conclusions: The comparison of different studies using different models cannot lead to deterministic conclusions. Any type of the vaccine should be generally considered cost – effective under certain thresholds. The additional costs of protecting by vaccinating the targeted population through the established screening program would be balanced by the potential savings from not having to treat diseases related to HPV. However, the results should be interpreted with caution. Decision makers must take into account the results, and also reconsider the price of the vaccine as it is´probably the factor that affects most the cost – effectiveness.

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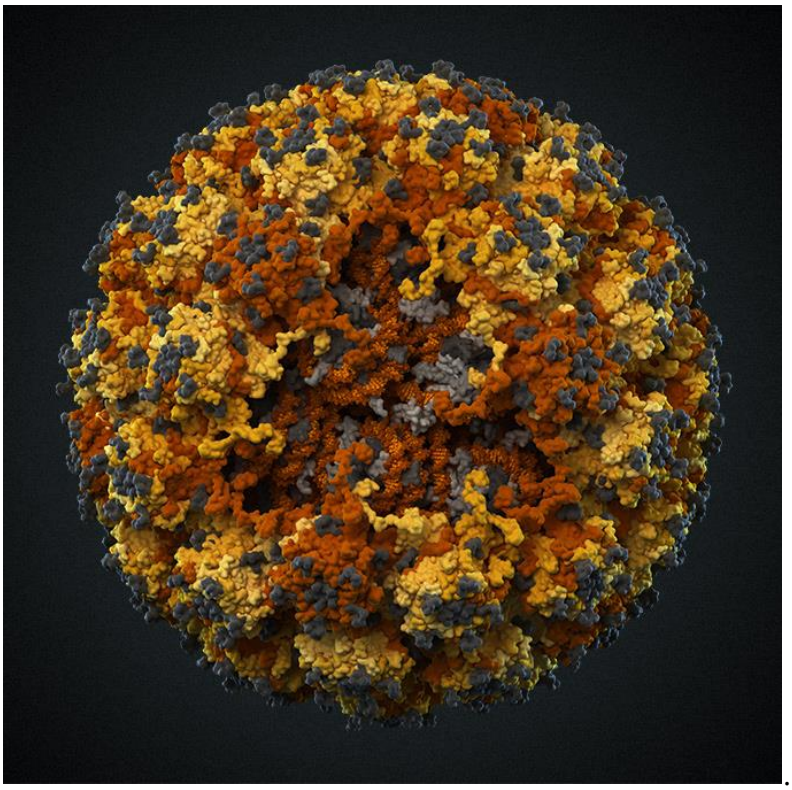
CHAPTER 1

GENERAL

HPV is the acronym for human papillomavirus. It is the most common sexually transmitted infection. There are more than 200 types of human papillomavirus (HPV). About 40 kinds can infect genital area —vulva, vagina, cervix, rectum, anus, penis, and scrotum also mouth and throat. HPV is transmitted through skin-to-skin contact or general sexual activity. A person can be affected by HPV, by having vaginal, anal, or oral sex with another person who has the virus. The most common way is by having vaginal or anal sex. HPV is very common: Most men and women get it at some point. The high-risk HPV typese3 cause approximately 5 % of all cancers worldwide. HPV can be transmitted even when an infected person has no symptoms. Symptoms may appear even many years after the initial infection, making it hard to know when this happened. Humans can be infected with multiple types of HPV simultaneously.



1.1 Historical background

HPV is a virus that has been afflicting humans and their ancestors for millions of years perhaps the oldest to afflict humankind. Back in ancient years, Soranus of Ephesus, a

Greek physician observed the existence of cervical cancer in women, caused by HPV[1]. Ancient Greeks and Romans also knew genital and skin warts (Oriel, 1971). Research about HPV started by McFadyean and Hobday in 1896, when they proved the transmission of warts in dogs (Rohan T. and Shah K. 2004) and 1907 Ciuffo proved the same in humans (Oriel, 1971). Important developments took place until '70s and in 1977 Gissmann, Pfister and Zur Hausen established the different types of human papillomavirus (Burd E., 2003).

1.2 Epidemiology

HPV is often cited as the most common sexually transmitted infection in the world:

Worldwide, the crude and adjusted HPV prevalences in women with normal cervical cytology were estimated to be 7.2% and 11.7%, respectively 10.4% (95% CI) (Bruni et al., 2010). The highest prevalences were estimated in Sub-Saharan African regions (24.0%),in Eastern Europe (24.1%) in Latin America and the Caribbean (16.1%) and in Southeastern Asia (14.0%). The lowest prevalences on the other hand, in Western Asia (1.7%) and in Northern America and Canada (4.7%).

The following figure shows the prevalence of HPV infections within women worldwide based upon the data found in the meta-analysis above[2].

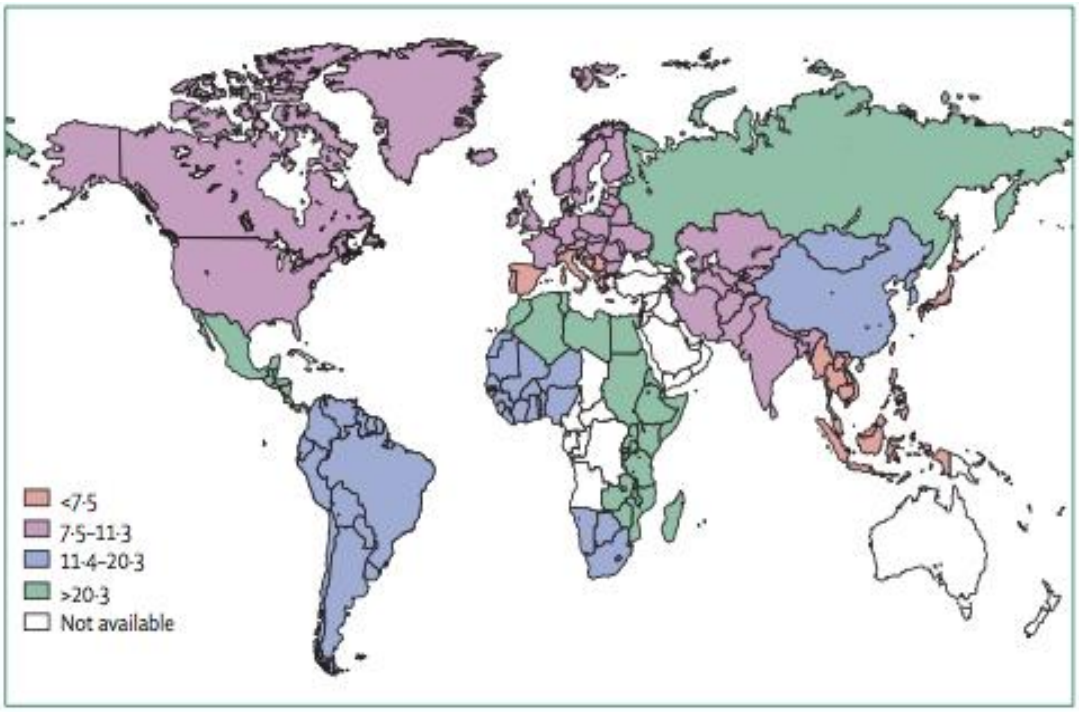


Figure 1: Prevalence of HPV infections infections within women

[1] https://www.britannica.com/biography/Soranus-of-Ephesus
[2] https://sites.google.com/site/hpvvirusproject/prevalence

The most common HPV types worldwide, were the high risk types: 16, 18, 52, 31, 58, 39, 51, and 56. The low risk type of HPV with the lowest frequency was type 6 in the American continent but 6HPV type was less common in Asia (0.2%) (Bruni et al., 2010). Compared with other types, HPV type 31 was very common in Europe (2.3%). Overall, 22.5% (95% CI) of HPV infections were estimated to be caused by type 16.

The HPV prevalences among different age categories were: for women <25 years of age 24%, 25-34 years old 13.9%, in some regions, the age with a slight increase in prevalence was 40 years but in general for women aged 35-44 the prevalence was 9.1%, 45-54 years old 4.2% (the lowest estimation) and for women older than 55 years 7.5%.

1.3 Risk Factors for Human Papillomavirus

Risk factors for HPV can be categorized by their origin, and if they are biologically or behaviorally based. (Dempsey AF., 2008)

Biologically Based	**Behaviorally Based**
Immunosupression	Lifetime number of sex partners
Coinfection with other STIs	Sexual History-Related Factors
Host Factors	Age of sex partner
HIV infection	Use of birth control pills
Micronutrient deficiencies	Frequency of condom use
Genetic polymorphisms	Recent new partner
Age at exposure to HPV	Marital status
Age at first menarche	Partner's number of partners
Viral Factors	Substance Use-Related Factors
HPV type	Alcohol use
Coinfection with multiple HPV types	Parity
Viral load	Current or previous tobacco use
	Current or previous drug use

Table 1 : Risk factors for HPV

1.4 HPV prevention

Condom use may lessen the risk for HPV and HPV associated diseases. A study among sexually active women demonstrated a 70% reduction in HPV infection when their partners used condoms consistently and correctly (Winer RL. et al, 2006) The surest way to prevent genital HPV infection is abstaining from sexual activity (i.e., refraining from any genital contact with another person). If someone is sexually active, the optimal choice is to be in a monogamous relationship with a partner who is uninfected. HPV

infection is so common that the majority of persons are infected (at some point of their lives) already, so no prevention or treatment strategies have been recommended for partners.

In order to prevent HPV associated diseases, most likely to have high efficacy are the prophylactic vaccines against HPV infection, as we will see in section 1.11.

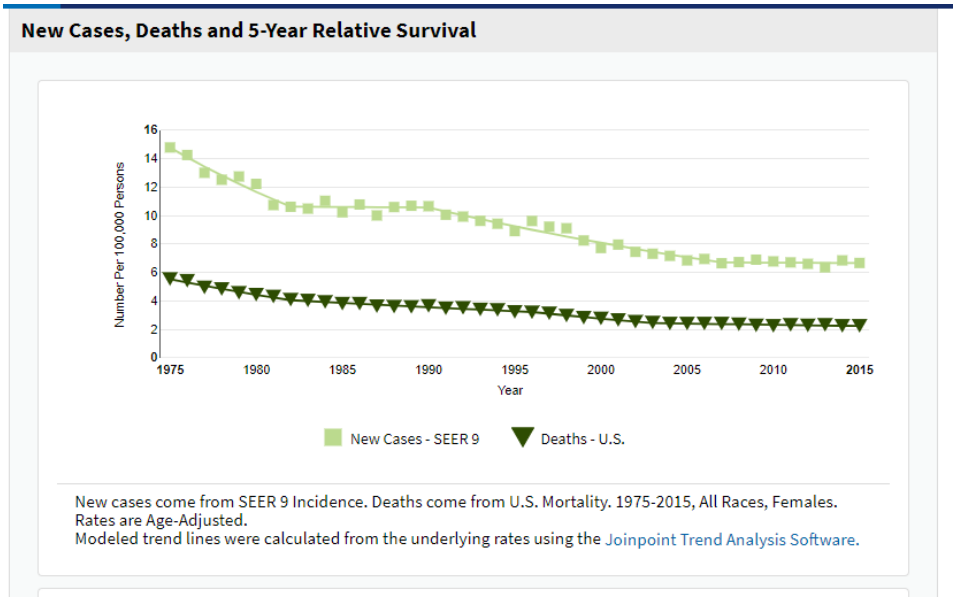


Figure 2: New cases and deaths related to HPV in U.S

1.5 Detection

The Papanicolaou (Pap) test, also known as Pap smear is a cost-effective widely used, method to screen for cancerous or precancerous condition on the cervix. The test was invented by Dr. Georgios Papanikolaou in 1928 (Tan SY., Tatsumura Y., 2015). Test results help doctors detect and identify abnormal cells and cell clusters that indicate the presence of a precancerous lesion or cancer and determine the possible treatments. Guidelines on how frequent a pap test should be performed vary from every one to five years (USPSTF, 2010). If the test detects abnormalities, it is necessary to be repeated in about one semester. In general, screening starts about some years after first woman's sexual relationship and continues until about the age 60, in many countries it is not necessary for non – sexually active women to be screened for HPV (Strander B., 2009). Pap testing normally isn't necessary after the age of 65 (unless there are recent abnormalities or related diseases) or after a total hysterectomy. People who have already been vaccinated against HPV are advisable to continue been tested because as we will see below, the vaccines do not protect of all HPV types that can cause cervical or other types of cancer (Arbyn M. et al., 2010). A pregnant woman can be injected with the vaccine from the 1st week till the 24th week of pregnancy. Pap test has been proved to reduce the probability death by cervical cancer up to 80% (Arbyn M. et al., 2010). A Pap test result can be normal (no cell changes are found on the cervix), unclear

(inconclusive result, known as ASC-US. The cervical cells could be abnormal. It is not clear if it is related to HPV) or abnormal. Abnormalities in the results of Pap test according to Bethesda system are (Nayar R., Solomon D., 2004):

- Atypical squamous cells of uncertain significance (ASC-US), some cells look abnormal, but it is impossible to distinguish if this is caused by infection or it is a precancerous situation, or generally related to HPV. Most of the time, in that case more testing is required.
- Atypical squamous cells where high-grade squamous intraepithelial lesion (HSIL) cannot be excluded (ASC-H), the cells seem abnormal but more testing is needed and perhaps treatment[3].
- Low-grade squamous intraepithelial lesion (LGSIL or LSIL), (the size, shape and other characteristics of the cells indicate that if a precancerous lesion is present)[4].
- High-grade squamous intraepithelial lesion (HGSIL or HSIL) (it is more possible that the lesion will develop into cancer, further screening is necessary[5].
- Squamous cell cancer or adenocarcinoma cells (the significant abnormality of the cells raises the probability that a cancer is present to almost 100%).
- Atypical glandular cells (AGC). When the glandular cells seem to be abnormal and could be cancerous, more testing is needed[4].

However, the primary use is for detecting invasive cervical cancer and cannot detect asymptomatic HPV infection. Furthermore, the accuracy of Pap test varies and depends on the age and screening history of the women Therefore, alternative tests are often used in combination with the traditional Pap test[5]. These tests include:

- HPV DNA test: testing for oncogenic HPV types (high risk types of HPV). HPV testing can be done using a range of technologies including DNA PCR, DNA hybridization, and testing for RNA.
- Colposcopy: A colposcopy is an examination of the vagina and cervix using a colposcope.
- Cervical biopsy: In a biopsy, a small amount of tissue is taken to look for precancerous cells or cancer cells.
- Endocervical curettage: A procedure, which the mucous membrane of the cervical canal is scraped using a curette.
- Cone biopsy: A cone-shaped sample of tissue is obtained from the cervix to check if abnormal cells are in the tissue beneath the surface of the cervix. Compared to a normal biopsy, this specimen is much bigger.

1.6 Types of human papillomavirus: Low-risk and high-risk

We can categorize HPV types into low-risk and high-risk.

[3] https://www.cancer.org/cancer/cervical-cancer/prevention-and-early-detection/pap-test.html
[4] https://www.mayoclinic.org/tests-procedures/pap-smear/about/pac-20394841
[5] https://www.hopkinsmedicine.org/health/treatment-tests-and-therapies/cervical-biopsy

Fifteen HPV types are classified as high-risk (16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82), 3 are classified as probable high-risk (26, 53, and 66), and 12 are classified as low-risk types (6, 11, 40, 42, 43, 44, 54, 61, 70, 72, 81, and CP6108).

Types 16 and 18 (which are the most aggressive types) are responsible for most HPV-related cancers. It is hypothesized that the high-risk HPV types cause a whopping 5% of all cancers worldwide.

1.7 HPV and associated diseases

- Warts. Warts are noncancerous skin growths. The virus triggers rapid growth on the skin's outer layer. They are most common in kids and are mostly found in fingers and in feet. They are not associated with cancer.
- Plantar warts. Plantar warts appear on the soles of the feet and can cause some pain.
- Flat warts. This type is more common in teens and children especially among females and can be found on the arms, face, legs and forehead.
- Genital Warts. Anogenital warts, medically known as condylomata acuminate, are the most common consequence of HPV infection. They are highly contagious: people may transmit the virus to others because they are asymptomatic. As mentioned before, types 6 and 11 are responsible for over 85% of warts (Woodhall S. et al., 2008) Genital warts have psychological and social consequences for the infected person furthermore charge the health care system, as they require constant management (Hoy T. et al., 2009).
- Cervical Cancer. HPV DNA can be found in almost all cervical cancers. (6). Cervical cancer is the second most common type of cancer diagnosed in women and is estimated to affect approximately 500.000 women each year. HPV types 16 and 18 cause almost 70% of cervical cancers and precancerous cervical lesions. The previous stage of the disease is cervical intraepithelial neoplasia (CIN) which is a precancerous condition in which abnormal cells grow on the surface of the cervix. The classifications of CIN are CIN I (mild dysplasia), CIN II (moderate dysplasia) and CINIII (severe dysplasia and carcinoma in situ).
- Anal Cancer. The prevalence of anal cancer is 1/100.000 so it is a rare but is a constantly increasing disease in developed countries[6]. It is more common in females than in males.
- Penile Cancer. Penile cancer is rare and mainly affects men aged 50-70 years. In more developing countries, the prevalence is much higher than in less developed.
- Vaginal and Vulvar Cancer. Vaginal cancer is a rare cancer, representing 2% of all cancers that affect females. Like cervical cancer, most of the cases are found in less developed countries. Vulvar cancer is rare among women worldwide,

[6] http://www.hpvcentre.net

with an estimated 27,000 new cases every year. Worldwide, almost over half of all vulvar cancer cases occur in more developed countries[7].

- Oropharyngeal Cancers. These are associated with high tobacco and alcohol consumption. However, further studies have shown a correlation between these type of cancers and HPV. According to new data suggests that type 16 of HPV is associated with tonsil cancer, tongue cancer and other oropharyngeal cancers[8].

  This table summarizes the HPV types and the related diseases:

Disease	**HPV type**
Common warts	2, 1, 7, 4, 26, 27, 29, 41, 57, 65, 77, 1, 3, 4, 10, 28
Plantar warts	1,2,4,63
Flat warts	3, 10, 26, 27, 28, 38, 41, 49, 75, 76
Genital warts	6, 11, 30, 42, 43, 45, 51, 54, 55, 70
CIN	High risk: 16, 18, 6, 11, 31, 34, 33, 35, 39, 42, 44, 45, 51, 52, 56, 58, 66
	Low risk: 6, 11, 16, 18, 31, 33, 35, 42, 43, 44, 45, 51, 52, 74
	Unspecified: 30, 34, 39, 40, 53, 57, 59, 61, 62, 64, 66, 67, 68, 69
Recurrent respiratory papillomatosis	6,11
Anal Cancer	16, 18, 31, 33, 35, 39, 45, 51, 52, 53, 56, 58, 59, 66, 68, 70, 73, 82 and others
Penile Cancer	16, 18, 33, 35, 6, 11
Vaginal Cancer	16, 18, 33, 31, 45, 52, 58 and others
Vulvar Cancer	16, 18, 13, 33, 52, 59,
Oropharyngeal Cancers	16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68

Table 2: HPV types and related diseases

1.8 Treatment

HPV is a virus, therefore there is not a treatment for its infection, however, for the diseases that can cause there are several cures.

About genital warts: topical creams directly to the skin or other invasive treatments such as cryotherapy, electrocautery, surgical excision and laser treatments can treat them[8].

[7] http://www.hpvcentre.net
[8] https://www.mayoclinic.org/diseases-conditions/genital-warts/diagnosis-treatment

About cervical cancer: cryosurgery, LEEP (loop electrosurgical excision procedure), surgical conization (a procedure in which a piece of tissue from the cervix is being removed using a scalpel or a laser or a combination of them)[9]. Also, in very severe cases hysterectomy can be performed.

About other types of cancer caused by HPV: The patients are treated exactly the same as the other patients who suffer from non HPV related cancer. The cause of the cancer doesn't affect the stages of the cure.

1.9 Cost Accounting

- Screening cost: pap-test cost for the general population.
- Furthermore costs in case HPV is detected: HPV-DNA test, colposcopy, cervical biopsy, and cone biopsy.
- Treatment costs: As said above, all types of treatment require a minimum cost. The most expensive treatment is hysterectomy and generally invasive procedures that include cervical amputation/destruction or cancer treatments (chemotherapy, surgeries) for other cancers.

1.10 Vaccines

Vaccines are a biological preparation that improves immunity to particular diseases[10] . Vaccines are made of weakened, killed, or fragmented microorganisms, toxins, antibodies or lymphocytes. It is the most effective method (and generally cost – effective) of preventing infectious diseases. They provide immune protection. Their effectiveness is being meticulously studied. Very rarely the protection they provide fail due to mostly clinical factors such as diabetes, HIV and other conditions in order the immune system is unresponsive. The efficacy of the vaccines depends on the disease, the age, any prior exposure to the disease, time since vaccination etc.

Vaccination is generally safe. However, there might be some adverse effects. (Stratton K. et al., 2011) The legislation set up a surveillance system for them, and provides information to consumers. Each possible adverse event is being studied and evaluated by the epidemiological, clinical, and biological evidence. There is no vaccine that is 100% safe, but very few adverse effects are shown to be caused by vaccines and these are rarely severe[11]. In that case, some countries such as the United Kingdom provide compensation for victims[12].

The World Health Organization monitors vaccination schedules worldwide, observing each country's program and general evidence on vaccination.

[9] https://www.cancer.gov/about-cancer/causes-prevention/risk/infectious-agents/hpv-fact-sheet#q6
[10]https://www.historyofvaccines.org/
[11] https://www.who.int/vaccine_safety
[12] https://www.gov.uk/vaccine-damage-payment

Greece's National Immunization Program shares similar characteristics with other European countries, follows the basic principles of The American Academy of Pediatrics but it is adjusted in the health and social conditions and in the epidemiological data of the country.

1.11 The HPV vaccine

The first HPV vaccine became available for females in 2006. It was also approved for males in 2010. In Greece, it was introduced in 2008.

There are 3 HPV vaccines: Gardasil, which protects against types 6,11,16,18 which are the most aggressive types of the virus and Cervarix, which protects against types 6 and 11, later a ninevalent vaccine became available, Gardasil 9v, which protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58 (see figure 4) (Herrero R. et al., 2015).

Below in the figure we can see the countries that have adopted HPV vaccination as a prevention strategy in their National Immunization Program as of November 2015 (Donken R. et al., 2016).

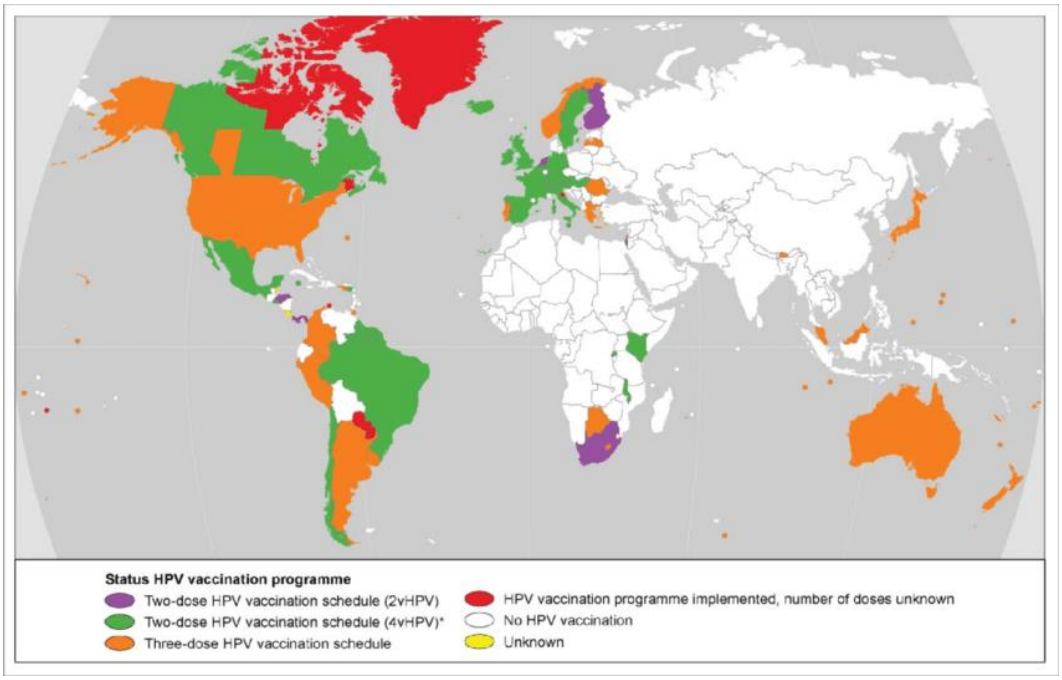


Figure 3: HPV vaccination programmes

All vaccines were examined thoroughly and were declared safe according to the WHO standards (Cortés J. et al., 2011). The World Health Organization recommends HPV vaccination as part of routine vaccinations in all countries. At least one of them it had been approved in 80 countries (including Greece) and mostly it is part of the each national vaccination program and financed by national healthcare systems. Two doses

of the vaccine are likely to be the most cost - effective option given that the provided protection lasts for at least 20 years (Jit M. et al., 2015).

Characteristics	Bivalent 2vVPH	Quadrivalent 4vVPH	9-valent 9vVPH
Commercial Name producer	Cervarix™, GSK	Gardasil™, Merck	Gardasil 9™, Merck
Types of virus like particles (VLP)	16 18	6 11 16 18	6 11 16 18 31 33 45 52 58
Dose of L1 protein	20/20 µg	20/40/40/20 µg	30/40/60/40 µg 20/20/20/20/20 µg
Adjuvant	ASO4 (500 µg aluminum hydroxide, 50 µg 3-O-deacylated-4'-monophosphoryl lipid A)	AAHS (225 µg amorphous aluminum hydroxyphosphate sulfate)	500 µg AAHS
Licensed schedules	0, 1, 6 month 0, 6 month	0, 2, 6 month 0, 6 month	0, 2, 6 month 0, 6 month

Figure 4: Types and characteristics of HPV vaccines

In the case of quadrivalent, approximately 90% of genital warts would never happen. (Schiller JT, Davies P., 2014). In 2007, Australia became one of the first countries to adapt a national vaccination programme using Gardasil in girls and young women. At the following figure, we can see that after 2007, the proportion of Australian females diagnosed as having genital warts at first visit, was dramatically reduced (Ali H. et al., 2013).

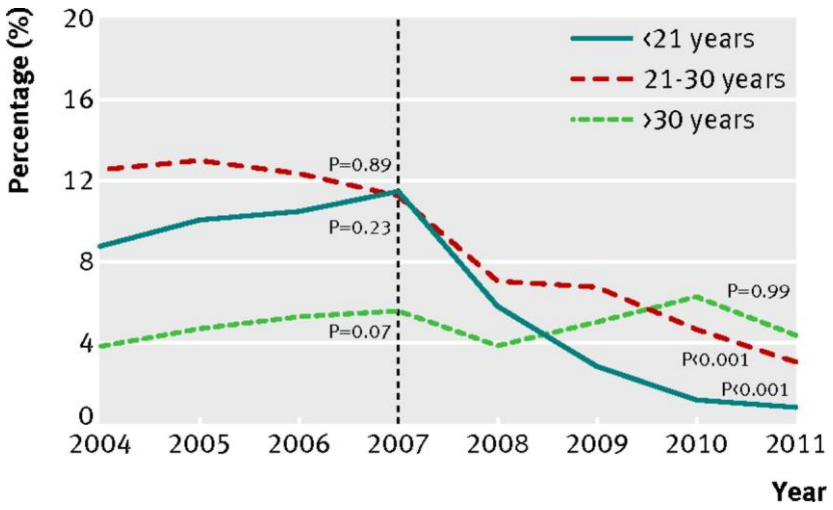


Figure 5: Percentage of Australian females diagnosed with genital warts

As we can see, the percentage of Australian women diagnosed with genital warts after 2007 is constantly decreasing. The vaccines will prevent about 70 percent of cervical cancers (Lowy D-R, 2016).

24 out of 55 countries that most likely have the least effect, have introduced HPV vaccine (Europe, USA and Canada). On the other hand, of 33 countries where HPV vaccines are likely to have the greatest effect, only four had introduced national vaccination (Jit M. et al., 2014).

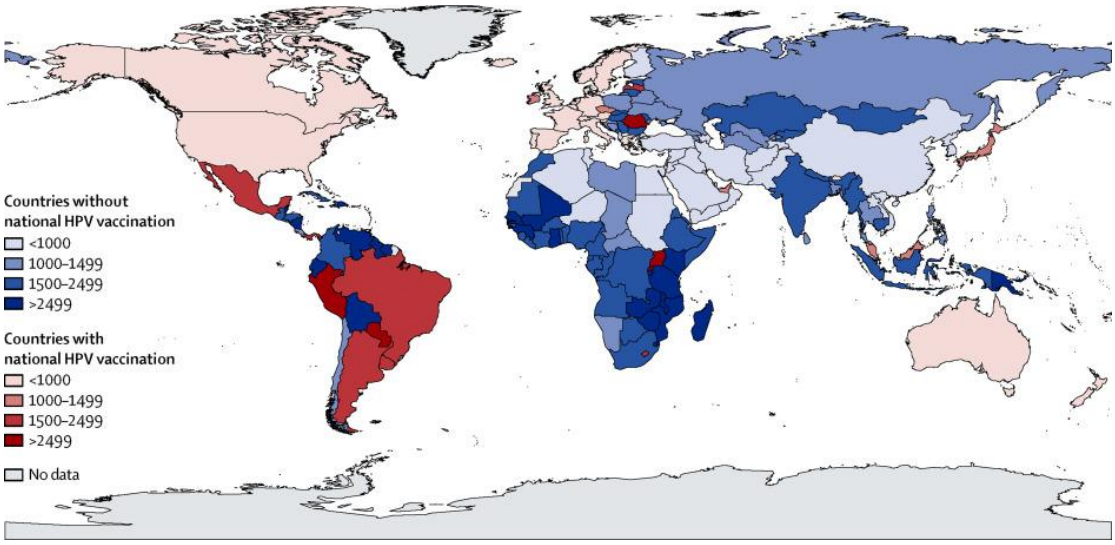


Figure 6: Estimated number of cervical cancers prevented per 100 000 girls vaccinated against human papillomavirus (HPV) in 186 countries.

The vaccines do not prevent other sexually transmitted diseases, and they cannot cure existing HPV infections or cancers.

The vaccine is relatively safe with no severe or harmful side effects. The most common of them include: redness, swelling or pain at the site of the injection, headaches, nausea, pain in the limbs, and high temperature[13].

In several countries, HPV vaccines have been approved for males due to the fact that they may reduce risks associated to HPV, such as the risk of genital warts and precancerous lesions and could result in the reduction of penile, anal and oropharyngeal cancers. However, vaccination of men is probably much less cost-effective than for women.

Through immunization programs, about 50 million women globally were vaccinated against HPV by 2015. This number represents 1.4% of the total female population and 6.1% of females aged 10–20 years (Bruni L. et al., 2016). In addition, 12 million women have received one dose of HPV vaccine, so to sum up: 59 million (95% CI) women worldwide have been vaccinated with at least one dose of HPV vaccine, 1·7% (95% CI) of the female population (Bruni L. et al., 2016).

[13] https://www.nhs.uk/conditions/vaccinations/hpv-vaccine-cervarix-gardasil-side-effects

Another interesting fact that is worth mentioning is that most women that have been vaccinated were not from low income countries but mostly from high-income or upper-middle-income countries (Bruni L. et al., 2016).

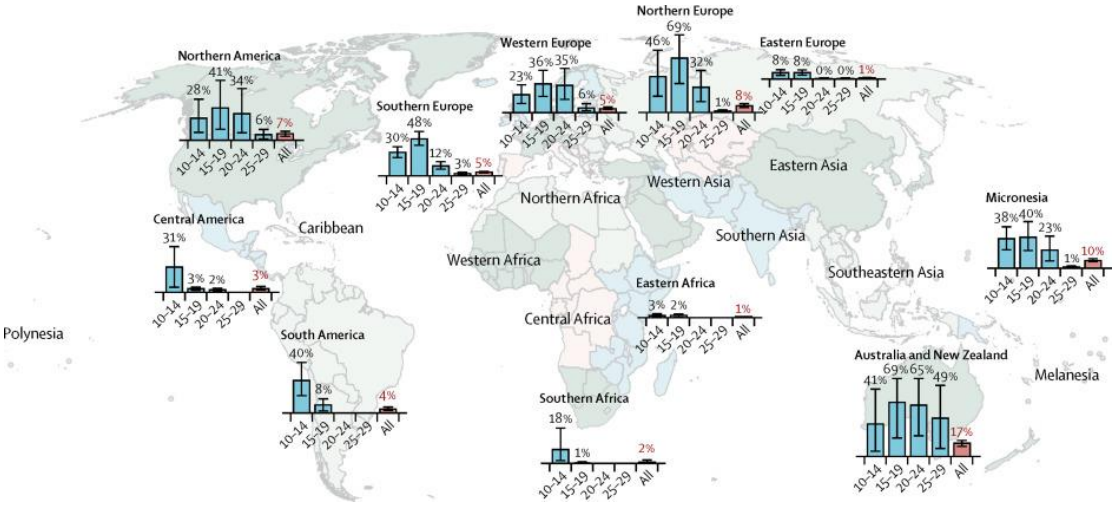


Figure 7: Estimated coverage of human papillomavirus vaccine (2 doses) by 2014, by age group and geographical region. (Error bars represent 95% CIs.)

The highest coverage rates were estimated in Northern Europe, Australia and New Zealand. Overall, In Northern Europe and in Northern America were estimated coverage rates of vaccination about 8% and 7% respectively. In Australia and New Zealand, the percentage of vaccinated women of all ages reached 17%. Regions with no or very low estimated coverage, have no bar charts.

1.12 HPV in Greece

In Greece according to a study (1) in women with normal cervical cytology, the prevalence of HPV in 2014 was 5.8% (95% CI) (Agorastos T. et al., 2014). The highest rates of a positive HPV-DNA test were found in women aged 25-29 and the most common type was HPV-16 (24.8%) followed by types 31, 35, 53 and others.

Almost 696 new cervical cancer cases are diagnosed in Greece every year making it the 12th leading cause of female cancer and the 4th most common female cancer in women aged 5 to 44 years[14]. Also the mortality tends to be high enough: About 271 cervical cancer deaths occur annually, so it is the 11th leading cause of female cancer and the 3rd leading cause of cancer deaths in young women[15]. A study in Greece amongst adolescents indicates that only about 10% are vaccinated (Vaidakis D. et al., 2017).

[14] http://www.hpvcentre.net/statistics/reports/GRC.pdf

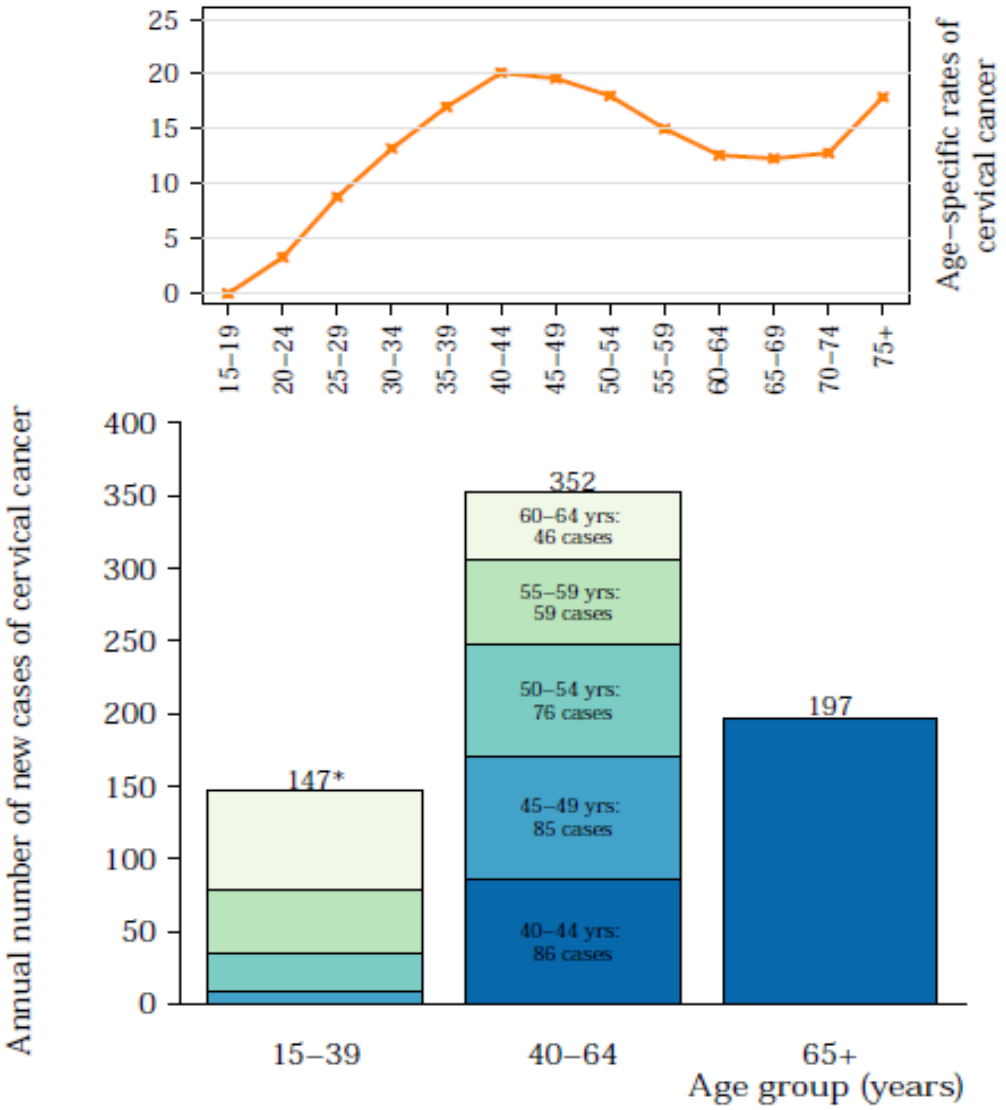


Figure 8: Number of cases per annum and age-specific incidence rates of cervical cancer in Greece

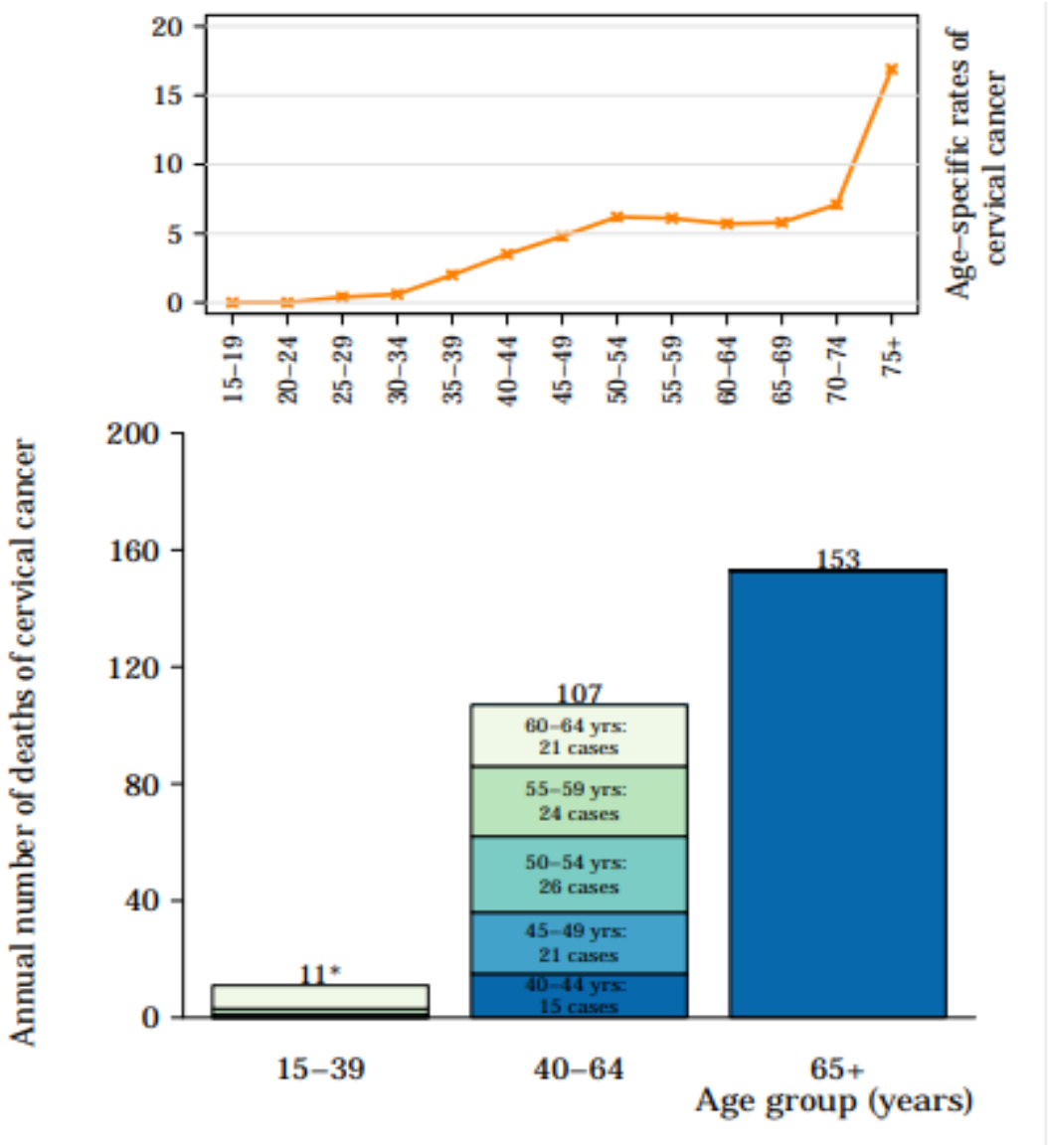


Figure 9: Annual number of deaths and age-specific mortality rates of cervical cancer in Greece

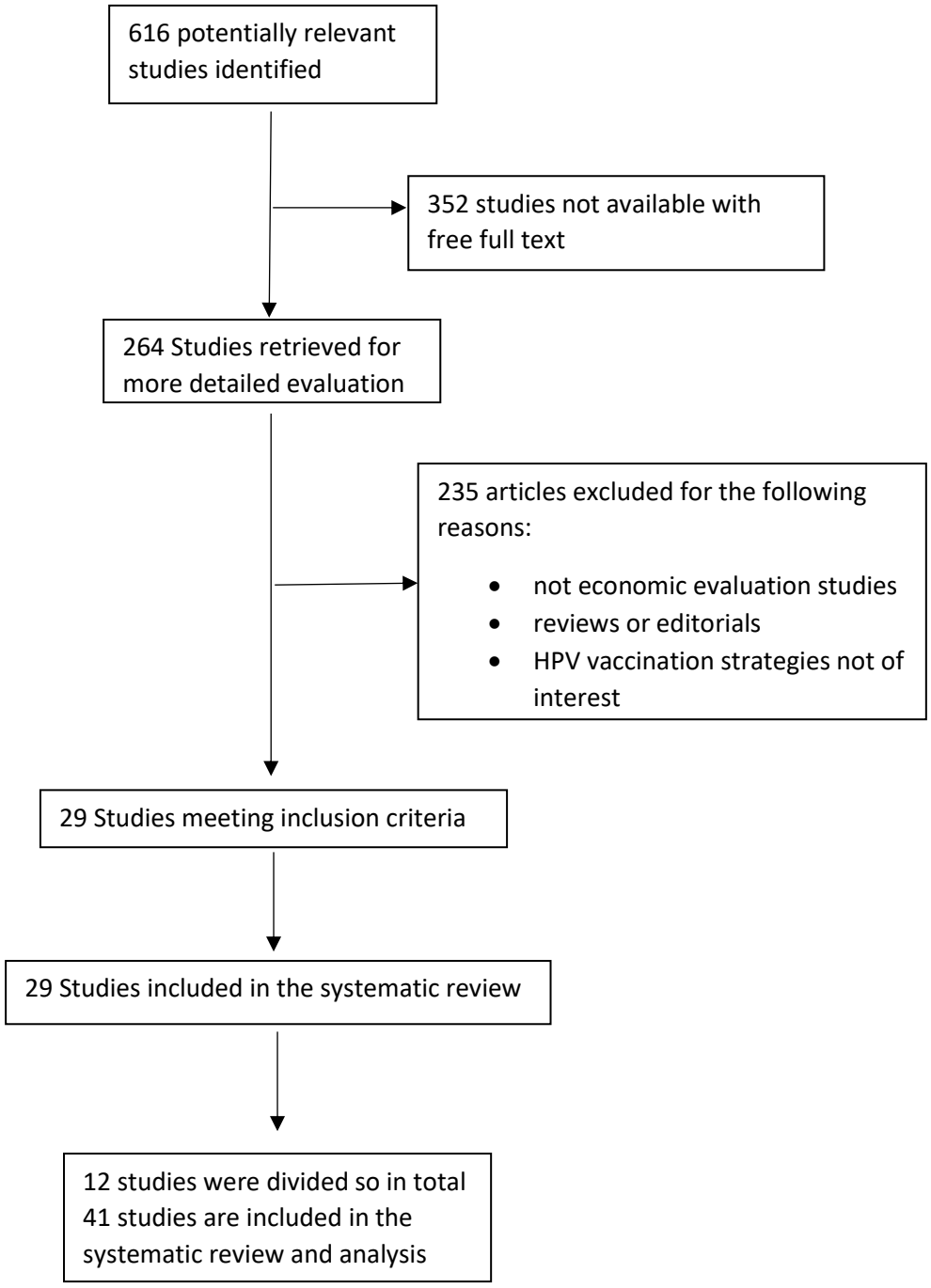
In January of 2008 both vaccines were introduced in the national vaccination program and in September of the same year IKA (the main public social security body) fully covered the cost for females aged 12-15 years old. Since January 2009, also has financially covered females aged 16-26 years old. The vaccination is given on demand through healthcare providers.

In Greece has never been conducted an economic evaluation for the HPV vaccine.

CHAPTER 2

METHODOLOGY

A systematic review of the literature was performed on 28 December 2018 through Pubmed and Cochrane Library. The following procedure was used for the search and selection of the relevant articles: initial assessment based on the title, abstract, and keywords, a full-text assessment and selection of the articles that fully corresponded to the inclusion criteria. The keywords that were used for the searching are: "cost-effectiveness" OR "cost utility" OR "economic evaluation" OR "economic impact" AND "HPV vaccine" OR "papillomavirus vaccine".



2.1 Inclusion and exclusion criteria

Studies examining the cost-effectiveness of HPV vaccine, considering both costs and outcomes measured in QALYs or LYG are included. Reviews, editorials, and conference abstract were excluded. Studies examining HPV vaccination strategies not of interest weren't included.
Studies written in any other languages other than English, or older than 10 years are excluded.

2.2 Quality assurance

The assessment of the articles was performed by using the criteria of Drummond (Drummond MF. Et al., 1997) for assessing economic evaluations, WHO's guide (Walker DG. et al., 2010) and and the CHEERS statement (Husereau D. et al., 2013).

2.3 The studies

The most important characteristics of the studies are summarized in table 3. The studies that are examined and analyzed are the following:
Jit et al (2008), Olsen and Jørgensen (2015), Luttjeboer et al (2013), Van Kriekinge et al (2017) , Brisson et al (2015), Chesson et al (2016), Blakely et al (2014), Drolet et al (2013), Kim (2009), Praditsitthikorn et al (2011), Obradovic et al (2010), Sharma et al (2012), Bresse et al (2014), Reynales-Shigematsu et al (2009), Annemans et al (2009), Termrungruanglert et al (2012), Lee et al (2011), Kawai et al (2012), Usher et al (2008), Yamabe et al (2013), Dasbach et al (2010), Torvinen et al (2010), Hillemanns et al (2008), Oddsson et al (2009), Yamamoto et al (2011), Kiatpongsan and Kim (2014), Liu et al (2010), Vanagas et al (2010), and at last Szucs et al (2008).

Some of the studies were divided because at the initial form of the matrix couldn't come to any significant conclusions. The divisions were made mostly based on the used unit (QALY or LY), the sex of the population (females separately from females) or the intervention (2V, 4V, 9V, or combinations).

Author	Year	Location	Income Category	Type of vaccine	Number of doses	Diseases	Type of model	Perspective	Time Horizon	Sensitivity Analysis	Most sensitive parameter	Vaccine price/dose	ICER	Conclusion	Population	Discount rate	Unit	FV(2018)	FV(2018)-USD
Jit	2008	UK	High	4V	3	CC, GW, AGC, OC	Dynamic	Healthcare payer	20y	One-way	Duration of protection	£80.50	£15094	Not c-e	12y.o F	3.5%	QALY	£21291	$27039.5
Jit	2008	UK	High	4V	3	CC, GW, AGC, OC	Dynamic	Healthcare payer	20y	One-way	Duration of protection	£80.50	£520255	Not c-e	12y.o F, M	3.5%	QALY	£733871	$932016.1
Olsen	2015	Denmark	High	4V	2, 3	CC, AGC, H/N , CIN 1, 2, 3	Dynamic	Healthcare payer	62y, 40y	One-way, multi-way	Discount rate, price	€ 123	€ 3.581	c-e	12y,o F	3%	QALY	€ 3.915	$4463.1
Olsen	2015	Denmark	High	4V	2, 3	CC, AGC, H/N , CIN 1, 2, 3	Dynamic	Healthcare payer	62y, 40y	One-way, multi-way	Discount rate, price	€ 123	€ 41.636	c-e	12y.o F,M	3%	QALY	€ 45.496	$51865.4
Luttjeboer	2013	Netherlands	Not stated	2V	3	Other cancer except CC	Markov	Not stated	lifelong	One-way,	Price, discount rate, cost of CC	€ 120	€ 5.815	c-e	12y.o F	3%	QALY	€ 6.741	$7684.7
Van Kriekinge	2017	Malaysia	Not stated	2V	2	CC, GW	Markov	Ministry of Health	Not stated	One-way, Two-way, PSA	Discount rate	Not stated, same for both vaccines	Not stated, 2V dominant	Both c-e	13y.o F	3%	QALY	NS	NS
Van Kriekinge	2017	Malaysia	Not stated	4V	2	CC, GW	Markov	Ministry of Health	Not stated	One-way, Two-way, PSA	Discount rate	Not stated, same for both vaccines	Not stated, 2V dominant	Both c-e	13y.o F	3%	QALY	NS	NS
Brisson	2015	USA	High	4V	3	CC, GW, OC	Dynamic	Societal	lifelong	One-way	Price	$145	$ 5500	C-e	13-17 y.o F,M	3%	QALY	$6010	$6010
Brisson	2015	USA	High	9V	3	CC, GW, OC	Dynamic	Societal	lifelong	One-way	Price	$158	$31100	c- e	13-17 y.o F,M	3%	QALY	$33983.8	$33983.8
Chesson	2016	USA	High	4V	3	CC, CIN1, 2, 3, GW, Other cancers	Dynamic	Societal	lifelong	One-way, multi-way	Time horizon	$145	$17,300	c-e	12-26 y.o F	3%	QALY	$18353	$18353
Chesson	2016	USA	High	9V	3	CC, CIN1, 2, 3, GW, Other cancers	Dynamic	Societal	lifelong	One-way, multi-way	Time horizon	$158	$8,600	c-e	12-26 y.o F	3%	QALY	$9123	$9123

Blakely	2014	New Zealand	High	4V	3	CC, CIN1, 2, 3, GW, Other cancers	Markov	Healthcare payer	Lifelong	One-way	Price	$113	$18,800	c-e	12y.o F	3%	QALY	$21159	$21159
Drolet	2013	Canada	High	4V	3	GW, CC, Other cancers	Dynamic	Societal	70 years	One-way, multi-way	Duration of protection, efficacy, price	CAN$95	CAN$15528	c-e	10y.o F	3%	QALY	CAN$18001	$13433.5
Drolet	2013	Canada	High	9V	3	GW, CC, Other cancers	Dynamic	Societal	70 years	One-way, multi-way	Duration of protection, efficacy, price	CAN$95	CAN$12203	c-e	10y.o F	3%	QALY	CAN$14146	$10556.7
Kim	2009	USA	High	4V	3	CC, CIN1,2,3, GW, Other cancers, resp.papillomatosis	Dynamic	Societal	lifelong	One-way	Vaccine coverage, efficacy	$120	$40310	Not c-e	12y.o F	3%	QALY	$52595	$52595
Praditsitthikon	2011	Thailand	Middle	2V	3	CC	Markov	Societal + healthcare payer	lifelong	PSA	Price	5000THB	8834 BTH	Not c-e	12y.o F	3%	QALY	10864 BTH	$340.1
Obradovic	2010	Slovenia	Not stated	2V	3	CC, CIN1,2,3	Markov	Healthcare payer	73 years	One-way	Booster dose, discount rates	$100	$23178	c-e	12y.o F	3%	QALY	$29361	$29361
Sharma	2011	Thailand	Not stated	Not stated	3	CC, CIN 1,2,3	Monte Carlo simulation(dynamic)	Societal	lifelong	One-way	Vaccine coverage, price	I$40	$7720	c-e	>9y.o F	3%	QALY	$9218	$9218
Bresse	2014	Austria	High	4V	3	CC, GW, Other cancers	Dynamic	Healthcare payer	lifelong	One-way	Discount rate	€ 110	€ 10,03	c-e	9y.o F, M	3%	QALY	€ 11.292	$12872.8
Reynales	2009	Mexico	Low - Middle	4V	3	CC, C1,2,3	Markov	Public healthcare provider	lifelong	Two-way	Age of vaccination, duration of vaccine, efficacy, cost	$45	Not Stated	c-e	12-25y.o F	3%	LY	NS	NS
Annemans	2009	Belgium	Not stated	4V	3	CC, GW, CIN1, 2, 3, related diseases	Markov	Healthcare payer	lifelong	Two-way	Discount rate, duration of protection	€ 130,22	€ 10.546	c- e	12y.o F	3%	QALY	€ 13.760	$15686.4

Annemans	2009	Belgium	Not stated	4V	3	CC, GW, CIN1, 2, 3, related diseases	Markov	Healthcare payer	lifelong	Two-way	Discount rate, duration of protection	€ 130,22	€ 13.756	c- e	12y.o F	3%	, LYG	17.948,00 €	$20460.7
Termrungruanglert	2012	Thailand	Not stated	4V	3	CC, GW, CIN1. 2, 3	Markov	healthcare provider	lifelong	One-way	Price, coverage	6189 BHT	160649 BHT	c- e	12y.o F	3%	QALY	BHT 191823	$6005.7
Lee	2011	Singapore	Not stated	4V	3	CC, CIN1, 2, 3 GW	Markov	healthcare provider	lifelong	One-way, Two-way	Vaccine effectiveness, coverage	SGD$400	SGD$9071	c- e	12y.o F	3%	QALY	SGD$11156	$8143
Lee	2011	Singapore	Not stated	2V	3	CC, CIN1, 2, 3 GW	Markov	healthcare provider	lifelong	One-way, Two-way	Vaccine effectiveness, coverage	SGD$400	SGD$12827	c- e	12y.o F	3%	QALY	SGD$15775	$11514.5
Kawai	2012	Brazil	Middle	4V	3	CC, CIN1, 2, 3, GW	Dynamic	Healthcare system	lifelong	One-way, multi-way	Duration of protection, price, discount rate	$15,15	$450/QALY(catch up)	c- e	12y.o F	3%	QALY	$537	$537
Usher	2008	Ireland	High	4V	3	CC, CIN1, 2, 3	Dynamic	Healthcare payer	lifelong	One-way, PSA	Discount rate, price, coverage	€ 100	7,383/LYG.	c- e	12y.o F	3%	LYG	9.922,00 €	$11311
Yamabe	2013	Japan	High	4V	3	CC, CIN1, 2, 3, GW	Dynamic	Healthcare payer	lifelong	One-way, multi-way	Duration of protection	¥36000	¥1,205,00(catch up)	c- e	12y.o F	3%	QALY	¥139692	$1287.1
Dasbach	2010	Hungary	High	4V	3	CC, CIN1, 2, 3, GW	Dynamic	Healthcare payer	lifelong	One-way, multi-way	Duration of protection	€ 93	€10,646/QALY(catch up)	c- e	12y.o F	3%	QALY	13,49 €	$15374
Torvinen	2010	Finland	Not stated	2V	3	CC, CIN1, 2, 3	Markov	Healthcare payer	lifelong	One-way, PSA	Discount rate, price	€ 77	€ 17.294	c- e	10y.o F	3%	QALY	21.907,00 €	$24973.9
Torvinen	2010	Finland	Not stated	2V	3	CC, CIN1, 2, 3	Markov	Healthcare payer	lifelong	One-way, PSA	Discount rate, price	€ 77	€ 35.806	c- e	10y.o F	3%	LY	45.357,00 €	$51706.9
Hillemanns	2008	Germany	Not stated	4V	3	CC, CIN1, 2, 3	Markov	Healthcare payer	lifelong	One-way	Duration of protection, discount rate	€143.8	€ 10.530	c- e	12y.o F	4%	QALY	15.586,00 €	$17768
Hillemanns	2008	Germany	Not stated	4V	3	CC, CIN1, 2, 3	Markov	Healthcare payer	lifelong	One-way	Duration of protection,	€143.8	€ 15.684	c- e	12y.o F	4%	LYG	23.216,00 €	$26466.2

										discount rate								
Oddsson	2009	Iceland	Not stated	2V	3	CC, CIN 2, 3	Static	Not stated	lifelong	Not stated	Discount rate, price	€ 163,02	€ 18.547	c- e	12y.o F	3%	QALY	24,20 €	$27586.8
Yamamoto	2011	Japan	Not stated	2V	3	CC	Markov	Societal	lifelong	One-way	Vaccine efficacy	¥58000(including visits)	8568182 ¥	not c- e	11y.o F	3%	QALY	10,537,783¥	$97095.5
Kiatpongsan	2014	Kenya/ Uganda	Not stated	9V	3	CC	Dynamic	Healthcare payer	lifelong	One-way, multi-way	Discount rate	Not stated	Not stated	c- e	12y.o F	3%	LYG	NS	NS
Liu	2010	Taiwan	Not stated	2V	3	CC	Markov	Healthcare payer	lifelong	One-way	Discount rate, vaccine immunity longevity	$121.3	$13674	c- e	12y.o F	3%	QALY	$17321	$17321
Liu	2010	Taiwan	Not stated	2V	3	CC	Markov	Healthcare payer	lifelong	One-way	Discount rate, vaccine immunity longevity	$121.3	$2,939	c- e	12y.o F	3%	LYG	$30325	$30325
Vanagas	2010	Lithuania	Not stated	2V	3	CC	Dynamic	Not stated	90 years	Not stated	Booster dose, vaccine penetration	Not stated	€397.31 (+booster/12y.o F)	c- e	12y.o & 15y.o F	3%	LYG	503,00 €	$573.4
Szucs	2008	Switzerland	High	4V	3	CC, CIN1, 2, 3, GW	Markov	Healthcare payer	lifelong	One-way	Need for booster dose, discount rate	CHF 236,85	CHF 26005	c- e	11y.o F	3%	QALY	CHF34948	$35297.4
Szucs	2008	Switzerland	High	4V	3	CC, CIN1, 2, 3, GW	Markov	Healthcare payer	lifelong	One-way	Need for booster dose, discount rate	CHF 236,85	CHF 45008	c- e	11y.o F	3%	LYG	CHF60486	$61090.8

Table 3: Summary of the studies included in the review

CHAPTER 3

ANALYSIS

3.1 General

The vaccination is still expensive for the low or middle income countries. 25% of the studies come from developing countries in contrast to 75% from developed countries.

The examined population in the majority of the studies is 12 year old females, but in many studies males were also incorporated.

25 out of 41 studies examined the 4V vaccine and its cost effectiveness analysis, while almost 30% examined bivalent vaccine. Only four studies investigated the use of ninevalent vaccine, USA twice (Chesson et al (2016), and Brisson et al (2015)), Canada (Drolet et al (2013), and in Kenya & Uganda (Kiatpongsan and Kim (2014)).

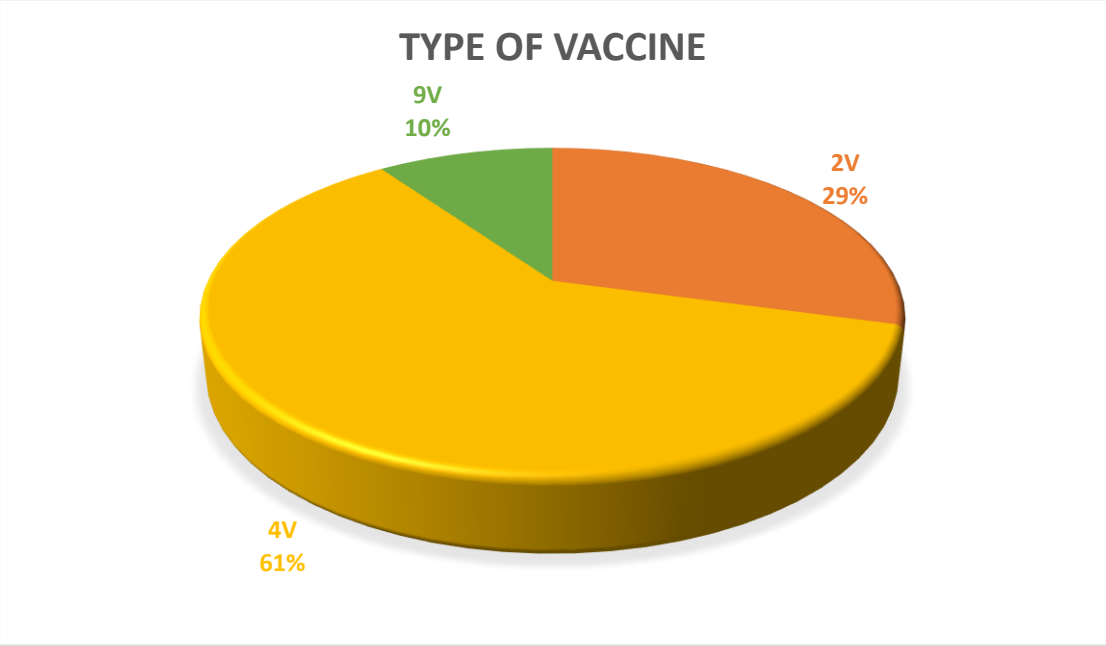


Figure 10: Percentages of different types of vaccine included in the review

The results of the most of the studies were projected up to 100 years in order to capture the associated diseases. As formentioned it is probable the disease to appear after, even years, the initial infection by the virus.

Nineteen studies use a dynamic transmission model in order to take into account indirect protection from HPV vaccination. Twenty one studies used the stochastic Markov model, only one study used static model so, there may be an underestimation in the health profit by HPV vaccination in this particular study.

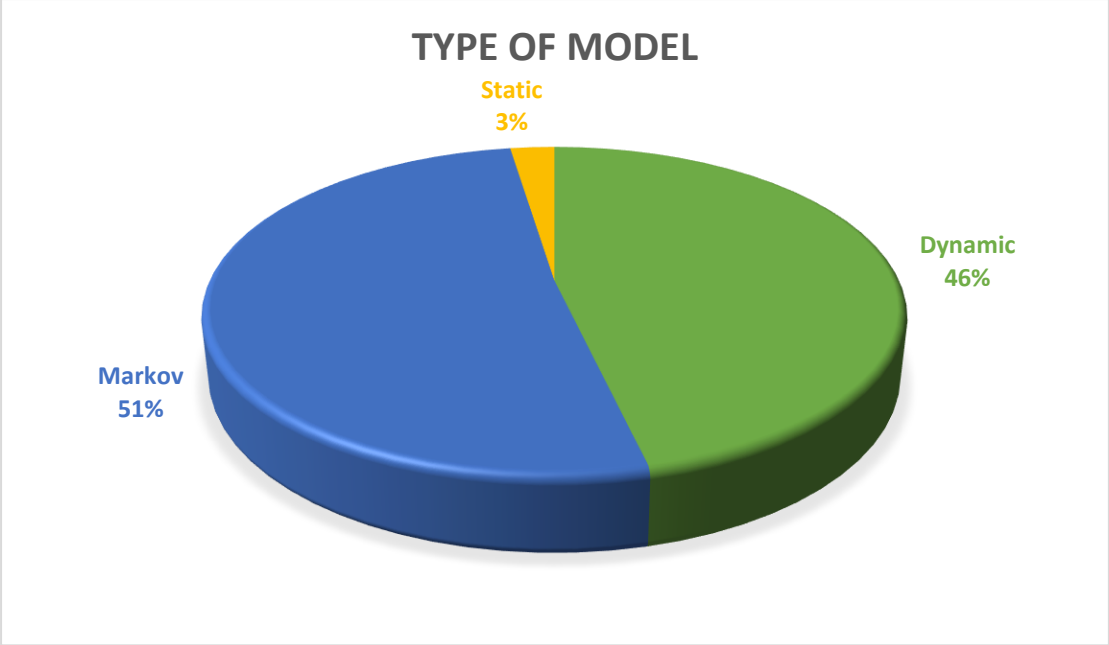


Figure 11: Percentages of type of models used in the review

Most countries, used their local currency in their cost-effectiveness analysis, while others in international or US dollars. The units of ICER as well as, vaccine prices per dose were all expressed to future value (December 2018) (19th column) and subsequently exchanged to US dollars according to exchange rate dated on 31th December, 2018 (20th column). Studies that have adopted the health care payer/provider (most of the times is the same) perspectives, only include direct costs such as vaccine cost, administration costs. The indirect costs usually are not investigated (productivity loss or loss of patient's time).
Most of the studies (most recent studies in USA, in Canada, in Thailand and in Japan) also adopted societal perspectives. The costs were estimated by information based on: on line searching, local data and general information, price of the vaccine defined by the government and literature

3.2 Effectiveness

The effectiveness of the vaccination programmes, in these studies is defined as the reduction mostly in cervical cancer, and generally the reduction of the prevalence of the diseases related to HPV for any type of vaccine.

3.3 Cost-Effectiveness

The units that were used to express cost – effectiveness, in the included studies are life-years gained (LYGs), or quality - adjusted life - years saved (QALYs). 32 studies used as unit QALYs and the rest 9 Lys. All of the studies examined the life - time risk of cervical cancer in the case of women and / or the reduction of the related diseases. The results are reliable given that the time horizon is sufficiently long. Most of the studies assumed that the vaccine is life-long, expect for Vanagas et al (2010), Szucs et al (2008). and Obradovic et al (2010) examined the case that a booster dose is necessary.

All the studies in this review compare at least one strategy to the current strategy adopted by the government and to the no intervention case.

As we can see all studies except for two conducted sensitivity analysis.35 studies used at least one way analysis, six of them conducted probabilistic sensitivity analysis and most of them a combination of one way, two way (multi way) and PSA analysis. At the sensitivity analysis that were conducted the most frequent sensitive parameter is the discount rate (almost everywhere is 3%), the vaccine price one of the major factors that contributes to the different incremental cost-effectiveness ratio (which is very reasonable), and at last vaccine's duration of protection.

Sensitivity Analysis	**Number of studies**
One way	35
Two way (Multi way)	17
PSA	6

Table 4: Types of sensitivity analysis used in the review

3.4 Results

Our goal, in this section, is to determine whether cost effectiveness is attributable to a set of key factors/variables. In other words, we will try to figure out the factors that affect if the HPV vaccine is cost effective or not. To determine that, we will utilize the probit model, which is a type of regression where the dependent variable can take only two values (in our case, cost effective and non-cost effective). The goal of the model is to estimate the probability that an observation with some particular characteristics belongs to a certain category.

Specifically, suppose that our binary dependent variable, y, takes on the values zero (non-cost effective) and one (cost effective). A simple linear regression of y on x (the vector of explanatory variables) is not appropriate, since among other things, the fitted value of y from a simple linear regression, which should lie between zero and one, can take values outside the [0 – 1] interval. So, we will use a specification that is designed to manage the requirements of binary dependent variables. Suppose that we model the probability that we observe the value 1:

$$\Pr(y_i = 1 | x_i, \beta) = 1 - F(-x_i'\beta)$$

where F is a continuous, strictly increasing function that takes a real value and returns a value in the [0 – 1] interval. Different choices for the function F, gives rise to different types of binary model. In our case,

$$\Pr(y_i = 1 | x_i, \beta) = 1 - \Phi(-x_i'\beta) = \Phi(x_i'\beta)$$

where Φ is the cumulative distribution function of the standard normal distribution. Our goal amounts to estimating β, the vector of coefficients, which is done by using the maximum likelihood procedure.

Our final sample consists of 41 data points (as mentioned above, before this section). From these 41 data points, 12% of them (5 results), belong to studies that showed that the vaccine is not cost effective and 88% (36 results), that showed that the vaccine is cost effective.

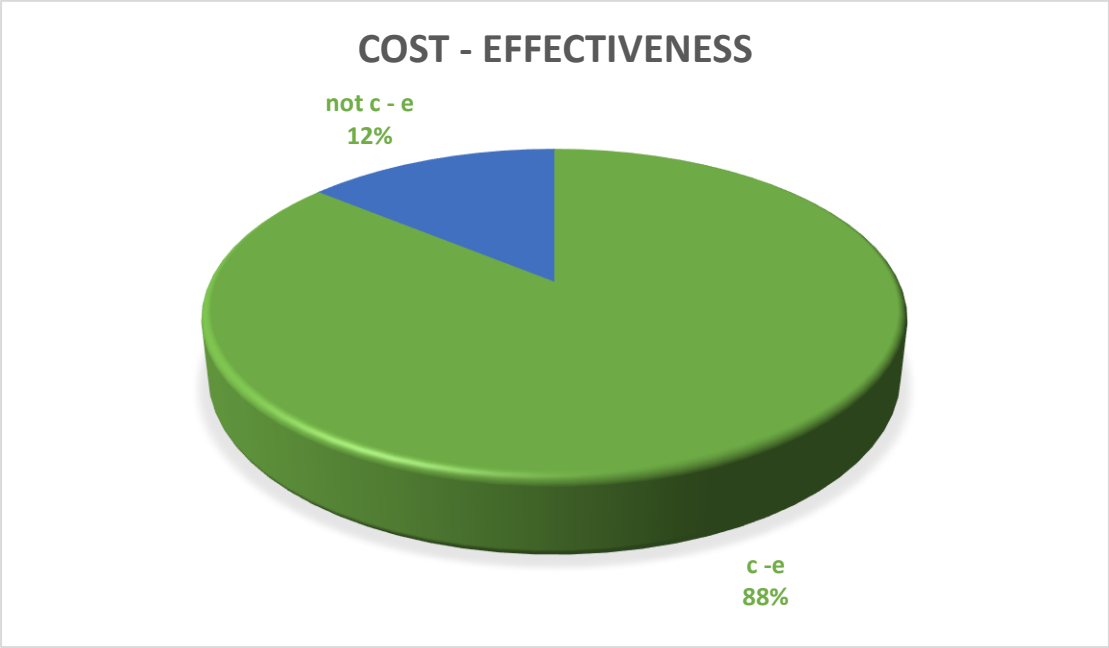


Figure 12: Percentages of different conclusions of the studies under review

The procedure we will utilize to detect the statistically significant factors, is the general-to-specific setting. More specifically, we begin by estimating a probit model with the cost effective/non-cost effective variable as our dependent variable, and with the following variables as the explanatory variables:

Variable Name	**Description**	**Values**
Year	Number of years prior to 2018	1 – 10
Developed	Whether a country is developed or developing	1 – Developed 0 – Developing
Income Category	Income Category	2 – High 1 – Medium 0 – Low
Perspective	Who conducted the research	3 – Public healthcare provider 2 – Healthcare payer 1 – Societal

		0 – Ministry of Health
Type of vaccine	Type of Vaccine	2, 4, 9
Type of model	Type of Model	0 – Static 1 – Dynamic 2 – Markov
Vaccine price 2018 $	Price of the vaccine adjusted for inflation and currency. All prices are at 2018 dollars.	54 – 1,947
ICER 2018 $	ICER adjusted for inflation and currency. All prices are at 2018 dollars.	340 – 932,016

Table 5: : Variables used in the statistical analysis

In the first step, we estimate the probit model with all explanatory variables included, and then drop the variable that is least statistically significant, i.e. its estimated coefficient has the smallest t-statistic in absolute value. We continue until the remaining variables have all a t-statistic larger than 1.64 in absolute value (which indicates that the variable is statistically significant at least at the 10% confidence level). The factors that seem to exhibit a statistically significant impact on the dependent variable are the following: Developed, Perspective, Vaccine price and Year. The table below presents the results of the final probit model.

Dependent Variable: CONCLUSION
Method: ML - Binary Probit (Newton-Raphson / Marquardt steps)
Sample: 1 41
Included observations: 35
Convergence achieved after 9 iterations
Coefficient covariance computed using the Huber-White method

Variable	Coefficient	Std. Error	z-Statistic	Prob.
DEVELOPED	1.607171	0.721818	2.226560	0.0260
PERSPECTIVE	2.292597	0.679596	3.373469	0.0007
VACCINE_PRICE_2018_$	-0.001545	0.000784	-1.969305	0.0489
YEAR	-0.751500	0.219896	-3.417524	0.0006
C	2.877867	1.668464	1.724860	0.0846

McFadden R-squared	0.462428	Mean dependent var	0.857143
S.D. dependent var	0.355036	S.E. of regression	0.293744
Akaike info criterion	0.726648	Sum squared resid	2.588573
Schwarz criterion	0.948841	Log likelihood	-7.716341
Hannan-Quinn criter.	0.803349	Deviance	15.43268
Restr. deviance	28.70814	Restr. log likelihood	-14.35407
LR statistic	13.27546	Avg. log likelihood	-0.220467
Prob(LR statistic)	0.010005		

Obs with Dep=0	5	Total obs	35
Obs with Dep=1	30		

Table 6: Results of the probit model

From the results above, we may conclude the following:

1- The positive coefficient of the variable Developed suggests that if a country is developed, then it is more probable that the vaccine is cost effective.

2- The positive coefficient of the variable Perspective suggests that if the research is financed by the healthcare provider or payer, then it is more probable that the vaccine is cost effective
3- The negative coefficient of the variable Vaccine price 2018 $ suggests that if the vaccine is more expensive, then it is less probable that the vaccine is cost effective. In other words, the higher the price of the vaccine the smaller the probability that the vaccine is cost effective.
4- The negative coefficient of the variable Year suggests that if the research was performed earlier, then it is less probable that the vaccine is cost effective. Older studies tend to suggest more often that the vaccine is not cost effective.

The McFadden R-squared which is equal to 0.462428, indicates that approximately 46% of the variability in the dependent variable, is explained by the model. This is quite a large percentage, especially given the fact that our sample is asymmetric, i.e. there are more studies suggesting that the vaccine is cost effective, compared to those that suggest that it is not.

Next, we carry out the Hosmer-Lemeshow and Andrews goodness-of-fit tests, in order to compare the expected values given by the model to the actual values, for each corresponding group/deciles. If these differences are "large" on average, this is an indication that the model does not fit the data sufficiently. The results are shown below:

Goodness-of-Fit Evaluation for Binary Specification
Andrews and Hosmer-Lemeshow Tests
Grouping based upon predicted risk (randomize ties)

	Quantiles of Risk		Dep=0		Dep=1		Total	H-L
	Low	High	Actual	Expect	Actual	Expect	Obs	Value
1	0.0680	0.5261	2	2.16742	1	0.83258	3	0.04660
2	0.5261	0.6631	1	1.57643	3	2.42357	4	0.34788
3	0.6701	0.7993	0	0.73579	3	2.26421	3	0.97490
4	0.8125	0.9194	2	0.53619	2	3.46381	4	4.61482
5	0.9905	0.9933	0	0.02570	3	2.97430	3	0.02592
6	0.9944	0.9959	0	0.01924	4	3.98076	4	0.01933
7	0.9967	0.9998	0	0.00589	3	2.99411	3	0.00590
8	0.9999	1.0000	0	0.00018	4	3.99982	4	0.00018
9	1.0000	1.0000	0	6.1E-06	3	2.99999	3	6.1E-06
10	1.0000	1.0000	0	5.5E-08	4	4.00000	4	5.5E-08
		Total	5	5.06685	30	29.9331	35	6.03554

H-L Statistic	6.0355	Prob. Chi-Sq(8)	0.6433
Andrews Statistic	27.5556	Prob. Chi-Sq(10)	0.0021

Table 7: Results of goodness-of-fit test

The two columns labeled "Quantiles of Risk" report the high and low predicted probability values for each decile. The next four columns report the actual and expected number of observations in each decile, while the last column reports the contribution of each decile to the overall Hosmer-Lemeshow (H-L) statistic. For each decile, the

larger the value, the larger the difference between the actual and predicted values. Reassuringly, only for the 4th decile, the H-L value is large.

At the bottom of the table statistics can be found. The table reports both the H-L and the Andrews test statistics. There exists some discrepancy between the p-values of the H-L and Andrews's tests, signaling mixed evidence. Specifically, for the former the p-value is large while for the latter is small (i.e. statistically significant at the 1% level). Furthermore, the relatively small sample sizes signal that the results should be interpreted with some caution.

Finally, the following table displays, for each explanatory variable, some descriptive statistics (mean and standard deviation). These statistics are computed for the whole sample, as well as for the two subsamples, conditional on the value of the dependent variable:

Variable	Mean Dep=0	Mean Dep=1	Mean All
DEVELOPED	0.800000	0.833333	0.828571
PERSPECTIVE	1.600000	1.933333	1.885714
VACCINE_PRICE_2018_$	918.4383	561.1027	612.1507
YEAR	8.600000	6.533333	6.828571
C	1.000000	1.000000	1.000000
Variable	**Standard Deviation Dep=0**	**Standard Deviation Dep=1**	**Standard Deviation All**
DEVELOPED	0.447214	0.379049	0.382385
PERSPECTIVE	0.547723	0.639684	0.631125
VACCINE_PRICE_2018_$	686.5231	339.5423	412.1633
YEAR	1.516575	2.648791	2.606392
C	0.000000	0.000000	0.000000
Observations	5	30	35

Table 8: Categorical Descriptive Statistics for Explanatory Variables

As can be seen from the table above, the mean value for the variables Vaccine price and Year is significantly different conditional on the dependent variable. Specifically, on average, for the cases where the vaccine is cost effective, the mean vaccine price is lower and the average number of years since the study took place is smaller, compared to the cases where the vaccine is not cost effective. Moreover, the variability for all variables depends on whether the vaccine is cost effective or not.

Overall, the aforementioned results suggest that our model captures a significant proportion of the variability in the dependent variable, with intuitive conclusions concerning the interpretation of the impact of the explanatory variables on the dependent variable. However, the small sample, suggests that results should be interpreted with caution.

CHAPTER 4

CONCLUSIONS

Given the fact that across different studies, the assumptions and the models used were diverse, this review contains heterogeneous results. Even more so, in some cases, even in the same country we can have different conclusions. For example in the case of USA, Brisson et al (2016) conclude that: Ninevalent vaccine is likely to be cost – effective strategy if the additional cost per dose is less than $13. On the other hand, Chesson et al (2016) suggests that, including males in the vaccination programme can improve health outcomes and can be cost-saving without no limitations. At last, Kim (2009) come to the conclusion that, a gender neutral vaccination programme, generally exceeded typical thresholds, so there is the need for further investigation.

In Canada, Drolet et al (2014) concluded that switching to the ninevalent vaccine is a cost – effective alternative to the quadrivalent vaccine, even in the case where ninevalent vaccine efficacy is 85%. However, most cervical cancers are caused by HPV types 16 and 18, so if ninevalent's efficacy against these types is proved to be lower than quadrivalent's is doubtful if it is going to be used.

The studies for Japan, see Yamabe et al (2013) and Yamamoto et al (2011), both indicate that the vaccine is cost-effective, although the perspective between them is different. The vaccination program for the female part of the population has been shown to reduce the occurrence of cervical cancer, CIN, and genital warts in Japan under the threshold set by the country.

In Asia, Van Kriekinge et al (2017) compared bivalent to quadrivalent vaccines in the area of Malaysia. Both of them are found cost – effective but bivalent is considered to be dominant over quadrivalent. On the other hand, Lee et al (2011) found the quadrivalent vaccine dominating the bivalent vaccine with greater estimated cervical cancer benefits and by reducing the incidence of genital warts in Singapore. In Taiwan Liu et al (2010) examined only the bivalent vaccine, which was found to be cost – effective, and emphasizes the need to improve the compliance rate of cervical screening, particularly for older females. In Thailand, Praditsitthikorn et al (2011) suggest that the most cost – effective strategy is by improving the existing screening programmes while Sharma et al (2011) conclude that a combination of the aforementioned strategy and a low cost vaccination could be the best policy. A reduction of the price of the vaccine is necessary. A year later, Termrungruanglert et al (2012) conclude that the nationwide coverage of HPV vaccination in the female part of the population is probably cost-effective in Thailand.

In Central Europe, Bresse et al (2014) in Austria, Hillemanns et al (2009) in Germany, Dasbach et al (2010) in Hungary and Szucs et al (2014) in Switzerland conclude that policies which include HPV vaccination are cost-effective based on thresholds that apply in these countries. All the above studies examined the cost – effectiveness of the quadrivalent vaccine.

In Western Europe, 3 out 4 studies examined the quadrivalent vaccine while Usher et al (2008) from Ireland examined the bivalent vaccine. All of the strategies were found cost – effective. In Belgium, Annemans et al (2009) concluded that even in the case that a booster dose is needed, the results remained cost effective. The study conducted in Netherlands by Luttjeboer et al (2013), shows that vaccinating the targeted population is a cost – effective strategy due to avoiding not only cervical cancer. Other cancers, vulvar, vaginal, anal and oropharynx cancers were taken into account.
In the UK, Jit's et al (2008) economic analysis indicates that vaccinating 12 year old females with the quadrivalent vaccine under a certain threshold is a cost – effective policy option assuming that the vaccine protection lasts more than 10 years.

In Northern Europe, in Iceland, Oddsson et al(2009) and in Finland, Torvinen et al (2010) examined the bivalent vaccine and found out that it was very cost – effective but the sensitivity analysis showed that this was sensitive to various parameters, mainly the discount rate and the price of the vaccine. In Denmark a more recent study by Olsen and Jørgensen (2015) indicates that a possible extension of the current HPV programme by including also males is a cost – effective strategy.

In Eastern Europe, in the case of Lithuania, Vanagas et al (2010) using a dynamic model suggests that the bivalent vaccine is a cost – effective strategy as it has many health and economic benefits. At the same conclusion came Obradovic et al (2010) in Slovenia. However, cost-effectiveness of HPV vaccination would become arguable in the case a booster dose is needed, in order to provide lifetime protection.

Both in Brazil, Kawai et al (2012) and in Mexico, Reynales-Shigematsu (2009) found the vaccine very cost – effective from the aspect of the national healthcare provider. The cost-effectiveness of the vaccination strategy was very sensitive to the cost of the vaccine, the age of vaccination, and the duration of vaccine efficacy.

Kiatpongsan and Kim (2014) in Kenya and in Uganda concluded that ninevalent vaccine is cost – effective in comparison to the current vaccination policy against HPV in Kenya and Uganda (bivalent and quadrivalent vaccines).

In New Zealand Blakely et al (2010), from the perspective of the healthcare payer and by using a Markov model conclude that the vaccine is cost – effective but also suggests that its price can be reduced in order to achieve cost - effectiveness and maximize health benefits.

Overall, the comparison of different studies using different models cannot lead to deterministic conclusions. Any type of the vaccine should be generally considered cost – effective under certain thresholds. The additional costs of protecting by vaccinating the targeted population through the established screening program would be balanced by the potential savings from not having to treat diseases related to HPV. However, the results should be interpreted with caution. Decision makers must take into account the results, and also reconsider the price of the vaccine as it is one of the most important factors that affect the cost – effectiveness.

CHAPTER 5

POLICY PROPOSALS

Even though no study has been conducted to examine the cost – effectiveness of HPV vaccines in the case of Greece, policy makers should consider the vaccination of males in the future, the type of vaccine currently in use by the national program, the number of doses that need to be received depending on the age of the vaccinated person and the vaccination of people older than 18 years old. Also, the price of the vaccine should be reconsidered. The very low vaccination coverage must be taken into account. There is a need for better awareness, education and effort to vaccinate the target groups as early as possible.

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