UNIVERSIDADE D COIMBRA FACULDADE DE MEDICINA

MESTRADO INTEGRADO EM MEDICINA – TRABALHO FINAL

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COST-BENEFIT OF HPV VACCINE IN THE PREVENTION OF CERVICAL CANCER IN PORTUGAL

ARTIGO CIENTÍFICO ORIGINAL

ÁREA CIENTÍFICA DE ECONOMIA E GESTÃO DOS RECURSOS DE SAÚDE

Trabalho realizado sob a orientação de:

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MAIO/2020

Faculdade de Medicina da Universidade de Coimbra

Custo-benefício da vacina de HPV na prevenção do Cancro do Colo do útero em Portugal

Cost-Benefit of HPV vaccine in the prevention of Cervical Cancer in Portugal

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Table of Contents

Abstract

Introduction: HPV is one of the most prevalent STI in the world and as such, we proposed to evaluate if there is a Cost-Benefit relation between the HPV vaccination programme and prevention of Cervical Cancer in Portugal.

Methods: We used the costs of vaccination against HPV within the PNV in the year 2019 (estimated at 3.217.360€) and compared them to the treatment costs of cervical cancer directly related to HPV (estimated at 3.394.160,39€), establishing a Net Benefit comparison.

Results: Was obtained a Net Benefit of 176.800,39€, which means the SNS will save about 176.800,39€ each year in treatment costs of cervical cancer because of the implementation of the HPV vaccination programme, being considered cost beneficial.

Discussion: Even obtaining a slim cost-benefit relation for the SNS, as the HPV vaccine prevents much more HPV related cancers other than cervical cancer, the cost-benefit of the HPV vaccine is potentially much more significant.

Conclusion: We concluded that exists a Cost-Beneficial relation in the implementation of the HPV vaccination programme for the prevention of Cervical Cancer in Portugal, and it should be studied for the other HPV-related cancers.

Keywords: HPV; vaccine; cost-benefit; cervical cancer; Portugal

Resumo

Introdução: O HPV é uma das IST mais prevalentes no mundo, por isso propusemos avaliar se existe uma relação Custo-Benefício entre o programa de vacinação contra o HPV e a prevenção do Cancro do Colo do Útero em Portugal.

Métodos: Usámos os custos de vacinação aplicados ao HPV dentro do PNV do ano 2019 (estimados em 3.217.360€) e comparámos com os custos de tratamento dos casos de cancro do colo do útero diretamente relacionados com HPV (estimados em 3.394.160,39€), estabelecendo uma relação de Benefício Líquido.

Resultados: Foi obtido um Benefício Líquido de 176.800,39€, o que significa que o SNS poupa cerca de 176.800,39€ por ano em custos de tratamento do cancro do colo do útero, devido à implementação do programa de vacinação contra o HPV, sendo considerado custo benéfico.

Discussão: Mesmo apresentando uma margem de custo-benefício estreita para o SNS, como a vacina contra o HPV previne muitos mais cancros associados a HPV do que apenas o cancro do colo do útero, o custo-benefício é potencialmente muito maior ao estimado.

Conclusão: Concluímos que existe uma relação custo-benéfica na implementação do programa de vacinação contra o HPV para a prevenção do cancro do colo do útero em Portugal. Recomendamos que deve ser estudada esta relação para outros cancros relacionados com o HPV.

Palavras-Chave: HPV; vacina; custo-benefício; cancro do colo do útero; Portugal

Background

The Human Papilloma Virus (HPV) is one of the most prevalent sexually transmitted infections (STI) in the world, infecting up to 80% of young women in the world and up to 90% of women some time in their lives[1].

HPV is responsible for multiple lesions in several systems[2-6]. It's considered to be the major cause of cervix uteri lesions and cervical cancer (about 100% of Invasive Cervical cancer lesions is infected with HPV[7]. It's also a major risk factor for other cancers, as of other organs of the female reproductive system (vulva and vagina), of the male reproductive organs (penis[8]); an agent in the development of most pre-cancerous anal lesions[9] and a percentage of invasive anal cancer lesions[10], and an important risk factor in the development of some head and neck cancer lesions (most notably of oropharyngeal cancer).

Facing an IST so prevalent around the globe, vaccination programmes[11-13] have been implemented in most countries. In most European countries, initially it was implemented the quadrivalent-vaccine, with a three-dose scheme for every 10 to 13-year-old girl and catch up schemes for girls as old as 17, as it was being implemented.

Since 2017, a two-dose scheme[14] regimen has been implemented, with a nonavalent vaccine (protects against 9 strains of HPV) directed at 10 year old girls. In recent years, several systematic reviews have been published[15] and the cost-effectiveness of extending the vaccination programme to all the boys in the same age group led to a medical consensus for increasing herd immunity and improving coverage in men who have sex with men (MSM), which are one of the risk groups who weren´t protected previously[16-18]. This will be implemented in Portugal from October of 2020, including a catch-up programme[19].

As for the detection of HPV infected women, and therefore secondary prevention of pre-cancerous cervical lesions, Portugal has employed, since the beginning of 2017, a population-based screening programme[20], directed to all females between 25 and 60 years old, using the nucleic acids search of HPV oncogenic serotypes every 5 years. If tested positive for the serotypes 16 or 18, the patient is referenced to a specialist consultation of cervical pathologies, and, if positive for other oncogenic types, cytology is proposed.

Almost all Portuguese women who present cervical pre-cancerous lesions and ICC are followed-up within the National Healthcare System (SNS). For these diseases, the patients are exempted of paying for medical care. Through this, the cost of diagnosis, treatment and follow-up is financed by the government[21]. The cost of treatment is regulated by ACSS (Central Administration for Healthcare systems) according to the severity of the disease (GDH)[22].

Considering the new planned HPV vaccination programme for the end of 2020, the question we pose is if the current vaccination programme is cost-beneficial for the SNS by preventing cervical cancer, as it is the main cancer affected by HPV and the most prevalent in Portugal of the HPV-related cancers. So, based on the yearly cost of treatment for this cancer and the cost of the vaccination programme, we propose a cost-benefit analysis of the HPV vaccine in the prevention of Cervical Cancer in Portugal.

Methods

Cost of Vaccination against HPV in Portugal

According to the updated 2020 National Programme of Vaccination (PNV), every pre-adolescent girl, from the age of 10 years old, should receive two doses of the nonavalent vaccine, within a 6-month interval.

The company selling the vaccine (Gardasil 9©) in Portugal is MSD®, and each retail dose costs 136,23€ (retail price for 2020[23]). This would make the cost for the HPV vaccination programme 272,46€ per person.

There is a protocol established between MSD® and the PNV, and according to several requests from ARS[24, 25] to buy vaccines from MSD®, the real cost for the SNS of each dose of the vaccine is 40,00€, for the year 2019. This cost will be the one used, considering the total sum of 80,00€ per person.

On average, 51.148 girls per year enrol in this programme (calculated using the INE[26] statistics for the estimated population by age group 10-14 years old, in the last five years with available data) and considering the limit threshold for herding immunity of HPV, according to the vaccination report cards published by the DGS[27] of 85% (the last three years have coverage above 90%, but will consider this threshold as stipulated by DGS), is recommended to vaccinate 43.476 girls, each year.

As registered in the SNS site, the number of administrated vaccines of Gardasil 9© in the year 2019[28], was 80.434. Considering that each girl must receive two doses of the vaccine to be effective, vaccines were administered to approximately 40.217 girls in 2019, which is 92,5% of the estimated. It will be the reference used for the number of girls vaccinated each year, as it is a more realistic number than the estimated, considering the variability of age difference in the age group 10-14 years females.

Considering these numbers, the estimated total cost for the SNS on HPV vaccination should be around 3.217.360€ per year.

Prevalence of HPV in Portuguese Women

Between 2008 and 2009, the CLEOPATRE study was carried out in several European countries, including Portugal, allowing the evaluation of HPV prevalence in Portuguese unvaccinated women. According to the first CLEOPATRE study[29], the general prevalence of HPV was 19,4%, and within the HPV positive ones, 76,5% were infected with high-risk HPV genotypes, with the most prevalent HPV genotypes being 16 (19.7%), 31 (11.8%), 53 (11.8%), and 51 (9.8%).

In the CLEOPATRE II[7] study the prevalence of HPV was determined in intraepithelial cervical lesions (CIN) and ICC, with an overall prevalence of HPV in these lesions of 97,9%, 95,5% in CIN2, 99,4% in CIN3 and 96,9% in ICC.

From this study, another article[30] concluded that 96,1% of these lesions were related to high-risk HPV genotypes infection and that the use of the nonavalent vaccine in Portugal would cover 93,2% of the HPV genotypes found in the samples.

Cervical Cancer in Portugal

In Portugal the most recent national data was from 2010[31], in which cervical cancer (C53) was the 9th most prevalent cancer in Portuguese women, with 746 cases during 2010, and an incidence rate of 11,3% (padronized for the European population). Most cases were diagnosed between 30 to 64 years old, corresponding to the recommended ages for regular screening. All these cases appeared in non-vaccinated women, as the HPV programme was only implemented in Portugal two years prior and none of these women met the criteria for vaccination at the time of implementation.

Cervical Cancer Stages

Cervical cancer is usually classified by the FIGO[32, 33] (International Federation of Gynaecology and Obstetrics) staging system for cervical carcinomas, which classifies it into four main stages, each with several substages.

In Portugal and most European countries there isn't any published data by government agencies on the incidence by stages of cervical cancer upon diagnosis, only the one-year and five-year survival percentage in each stage[34].

As such, our research included several clinical studies in which they used stages at the time of diagnosis as one of the variables[35-40]. From the research, we selected a case-control study performed in the United Kingdom[41] because of the similarities of the two health care

systems[42, 43] (founded in the same principles and with the same main infrastructures) and the cervical screening programme in both countries was similar at the time the study was conducted.

The histopathological results were taken from databases between 2007 and 2013, years close to the last public results published in Portugal, with results categorized following the FIGO staging system from 2009 (with some small differences between substages, not affecting the classification of the groups used in the study). The results were 37,5% for stage 1A (most cancers are diagnosed at this stage because of the regular screening methods), 35,1% for stage 1B, 14,9% for stage 2 and 12,5% for stage 3+ (includes stages 3 and 4, which are a minority in the identified cases at diagnosis).

Treatment Costs for Cervical Cancer on SNS

According to the table of costs of treatments in the SNS (the last year available), published by ACSS[22] and in *Diário da República*, and through analysis of the cost of treatment of cervical cancer by the attributed codes GDH 512 (surgical) and 530 (medical), we selected the GDH 512, as already includes all the medical costs in their final value. Each GDH has four grades of severity attributed to them (from 1 to 4) and establishing a relation to cervical cancer, we attributed each stage of cancer (used in the study which we collected the stages sample) the corresponding grade of severity.

In Table I the treatment costs for each stage are presented, according to the respective GDH, and the total treatment costs for all ICC in Portugal each year, was estimated at 3.758.343,91€.

Table I: Treatment Costs of ICC, according to each stage

Stage	Severity grade of GDH - 512	Percentage of cases at the time of Diagnosis	Number of cases translated to the Portuguese Reality	Cost per case at each stage	Total estimated cost of each stage
IA	1	37,50%	279,75	2.121,85 €	593.587,54 €
IB	2	35,10%	261,846	2.571,77 €	637.407,69 €
II	3	14,90%	111,154	6.816,38 €	757.667,90 €
III +	4	12,50%	93,25	18.977,81 €	1.769.680,78 €
Total					3.758.343,91 €

Cost-benefit Analysis

For this study a cost-benefit analysis (CBA) was selected, based on the similarities between the two most commonly used methods of analysing the benefits of introducing healthcare measures (cost-effectiveness and cost-benefit) and the differences of results obtained from such methods[44, 45].

For the cost-effectiveness analysis, we usually would need two methods to compare between for the prevention of cervical cancer, to which there's no alternative method at the moment besides vaccination, evaluate the Quality-adjusted life-year (QALY) attributed to the vaccination programme for HPV and consider the willingness of the population to pay for the programme. At the moment, we didn´t have the means to evaluate the attributed QALY, and the willingness to pay is not applicable in this situation, as the PNV is entirely paid for by the government.

A CBA evaluates every aspect of the costs and benefits of the measure, attributing a monetary value to every aspect. In this study it is possible to evaluate the direct costs of vaccination and treatment for cervical cancer. Unfortunately, the several indirect costs associated with the prevention (time spent by nurses administering the shots, etc.) and with diagnosis and treatment (missing days at work, time spent at consultations, impact on alterations of the family dynamic, etc.) won´t be considered.

The costs for cervical cancer screening weren´t considered as a variable because the screening programme will keep going for the next several years, with no plan of being altered or removed. It will probably remain a constant through the next few years and does not influence the direct costs of diagnosis and treatment of cervical cancer.

As such, in the HPV Prevention Costs was considered the cost of vaccines against HPV for the PNV, with the acquisition of the vaccine at the agreed price for the girls' group in each year (an estimated 3.217.360€), and designated as B.

For the Treatment Costs were considered the costs defined by ACSS, an estimated 3.758.343,91€ per year, as presented in Table I.

We considered 90,31% of these costs regarded as benefits if eliminated by the vaccine, because 96,9% of ICC are attributed to HPV[7], and 93,2% of these HPV genotypes[30] are covered by the vaccine, and the efficacy of the vaccine was considered as 100% for this study (upper estimation), as there wasn´t yet confirmed the long-term efficacy[46, 47] in the women who received the first vaccine (bivalent at the time).

So, the Treatment Costs associated with ICC that would be eliminated by the vaccine programme should be 3.394.160,39€ approximately, each year, designated as A.

In a CBA analysis we could choose to calculate the Benefit/Cost Ratio or a Net Benefit. It was selected the Net Benefit, which is a direct subtraction to the Net Benefits (direct costs of treatment associated with ICC - A), the Net Costs (the HPV vaccination programme - B), to calculate the Cost-Benefit of HPV vaccination programme in the prevention of Cervical Cancer, resulting in the following formula:

Net Benefit = Net Benefits – Net Costs

Net Benefit = ICC Treatment Costs - HPV Prevention Costs

So, the final formula is:

Net Benefit = A – B

Results

Applying the formula to the costs that we have:

Net Benefit = A - B

Net Benefit = 3.394.160,39€ - 3.217.360€

Net Benefit = 176.800,39€

The Net Benefit between the HPV Prevention Costs and the ICC Treatment Costs is of 176.800,39€. It is considered cost-beneficial, because there is net benefit superior to 0 (Net Benefit > 0), which means the benefits on savings are superior to the costs.

This number represents a saving of 5,4%, considering the costs of treatment directly related to the HPV infection. This means that by each euro invested in the vaccination programme, extra 0,05€ will be saved.

This means that each year, the SNS will save approximately 176.800,39€ in expenses that would be direct to the treatment of ICC in the future, by applying the HPV vaccination programme in the present.

This will not have a direct impact in the present, as most women diagnosed with ICC now haven´t been vaccinated, because they weren´t included in the programme when it first started (didn´t have the recommended age). We will be able to observe these results in a near future, as the first vaccinated women will be included in the screening programme this year or next year, and in five years they will reach the main time period of their lives where are at the most risk of developing ICC by the HPV infection.

So, even being cost-beneficial, the first monetary benefits will only be visible after a decade and a half of the implementation of HPV vaccination programme and will take more than two decades to see this full result.

Discussion

Even with the Net Benefit confirming that the HPV vaccination programme is beneficial for the SNS on the long-term, there were several years where the overall cost will be significantly bigger, while the cases of ICC of non-vaccinated women are treated and implement the vaccination programme.

At the moment, the first vaccinated girls are entering the screening programme and, if the efficacy of this vaccine is demonstrated, most of the treatment costs will drastically reduce in the next few decades, as more vaccinated women enter the screening programme. At that point, the costs spent on vaccines in the first decade will be compensated by the money saved in treatment costs.

From a directly economic point, there isn´t a major justification to implement the HPV vaccination programme to just prevent Cervical Cancer, as the Net Benefit is so small, considering the budget for the SNS and without many lucrative profits, according to the GDH.

However, several limitations in the calculus for the HPV vaccination programme and the treatment costs can influence the final result of the Net Benefit and should be considered in the analysis of the final result.

Some indirect costs associated with the HPV vaccination programme weren´t considered in the final cost, as the nursing act of administering the vaccine, because we couldn´t calculate the yearly costs of the nursing acts of administering the vaccine on the target population.

This was considered an indirect cost on the vaccination programme because the nursing labour is paid most of the time as fixed income (most nurses are contracted under a permanent contract with the SNS), and the time spent in this act would be allocated elsewhere, making it difficult to estimate the total amount (because there isn´t a time slot allocated especially for vaccination in most nurses' schedules). If considered as a direct cost, it would limit the cost-benefit of the vaccine, reducing the Net Benefit, and could even turn out a negative balance, and the measure wouldn´t be considered cost-beneficial.

The Vaccination Programme can also have small variations in their total cost, as the number of girls who enter the programme in the last decade has decreased because the birth rate in Portugal has gradually decreased in the last two decades. As such, this small decrease in the vaccination costs can slightly increase the Net Benefit in the short term. Considering this

aspect, in a larger time frame, the Net Benefit would possibly reduce the total cost, but remain positive. This occurs as the number of women vaccinated and the number of ICC cases decrease at an equal rate, as the total number of women in Portugal decrease through the decades.

The Treatment Costs we considered don´t take into account all the indirect costs that influence the final result, because they couldn´t be evaluated. The comorbidity and mortality factors in those women may have more impact than simply the medical costs, for example, the decreased work productivity (missing workdays, time spent at consultations, etc.) and impact in family dynamic (time spent accompanying the patient throughout the treatments, including missing days of work, more time spent at domestic work, etc.). These aspects, if able to calculate their total value, would be significant and substantially increase the treatment costs, increasing the final value of the Net Benefit and making HPV vaccination significantly more cost beneficial.

Also, considering the low number of ICC cases registered each year in Portugal (as of 2010) and the small latency of these cases to be discovered, as most of them are detected early by the screening programme if the women are followed at a regular basis, means that most pre-cancerous lesions are treated at that stage. This prevents them from achieving an ICC status, reducing the number of cases and treatment costs associated. If the screening programme wasn´t implemented, the number of ICC cases would be much higher, as the treatment costs and the final Net Benefit would be superior.

The Cervical Cancer data at the national level in Portugal hasn´t been updated since 2010, and the percentage of a certain stage at the time of diagnosis can be different from the study selected, as there is no available information about this data in Portugal. Because of this, Treatment Costs can be underestimated or overestimated, modifying the Net Benefit negatively or positively. The Treatment Costs can also be underestimated because as the screening programme is better implemented, it increases the number of cases detected and the associated costs with ICC.

If we didn´t know the real cost of the Gardasil 9© vaccine to the PNV, and we only used the commercial price published by Infarmed, the vaccination costs would increase significantly in an artificial way and thus limiting the potential cost-benefit the vaccine has, making the Net Benefit significantly negative and not be cost-beneficial at all.

The Screening Costs, if considered in the analysis, would underestimate the Net Benefit if it was included as part of the prevention programme, but as it is already implemented and will be continued for the foreseeable future, it won´t influence the method used for prevention. The Screening Costs could also increase the estimated treatment costs if considered as such and

increase the Net Benefit, because it is already done as the first step in the diagnosis of cervical cancer to all women, independently of the clinical suspicion of ICC.

The Treatment Costs will reduce over time, as the first women vaccinated enter the screening age and decrease their risk of having ICC, but the risk will never be completely eliminated as is highly improbable the vaccine has a 100% efficacy, and some ICC doesn´t have a correlation to the HPV infection.

So the Net Benefit will decrease in the next few decades, after the initial increase, as more women will not present HPV infection (not only propelled by the decreasing number of HPV infections in women, but also by the herd immunity that men will acquire when they start their vaccination programme) and the number of cases of ICC associated with HPV will drastically reduce.

However, the Net Benefit for a single person will always be positive, as the treatment costs will always be superior to the vaccine for that person, remaining the Cost-Benefit of the HPV vaccine a constant at the individual level.

The Screening Costs will also be reduced by the implementation of the vaccination programme because it will reduce by almost 19,4% (considering an effectivity of the vaccine of 100%) the women tested positive for HPV, and even as the first step of screening is maintained (HPV genotype searching), the next steps for searching for cervical lesions wouldn´t be necessary, as most women would test negative for HPV infection.

The HPV genotypes distribution will modify over time with the increasing prevalence of sexually matured women who received the vaccine, which can modify the efficacy of the current vaccine, and thus the prevalence of the most frequent HPV genotypes in ICC, decreasing the benefits associated to the vaccination programme. Alas, this modification will only have an impact after a few decades of the HPV vaccination programme applied.

We only considered the Cervical Cancer to evaluate the Cost-Benefit of the HPV vaccination programme on girls because we don´t have information available on the staging distribution of the other cancers at the time of diagnosis to attribute them to their GDH severity. If we were able to consider all the other cancers associated with HPV (Vulva, Vagina, Penis, Anal, Head and Neck), the Treatment Costs would be ten-fold higher, and the total Net Benefit would be much higher.

We also didn´t consider the pre-cancerous lesions CIN, precursors of ICC, because we don´t have the total number of CIN2 and CIN3 detected each year in Portugal. If they were considered, the Treatment Costs would increase (even if not that significantly, because their

treatment is cheaper, as involves fewer techniques and less follow-up), and by default increase the Net-Benefit.

Considering these last two assumptions, the HPV vaccination programme may be significantly more Cost-beneficial, because the increased treatment costs would surpass the HPV vaccination programme by millions of euros and significantly increase the Net Benefit total.

The insertion of the pre-adolescent boys on the HPV vaccination programme by October of 2020 will increase the prevention costs by millions of euros. This will, if only considered the evaluation of the Net Benefit for the ICC, drastically decrease the Net Benefit Total and will not be cost-beneficial. So we recommend, if this evaluation will be made, to consider all-male HPV related cancers in the analysis.

Considering the slim Net-benefit obtained, related only to the ICC, it limits a real evaluation of the Cost-Benefit of the HPV vaccine. We recommend in a posterior evaluation, to consider all HPV related cancers and pre-cancerous lesions treatments in the treatment costs, and consider all the HPV vaccine-related costs, with the introduction of boys in the programme.

Conclusions

With the available data, the HPV vaccination programme is considered Cost-Beneficial, on a slim scale to the SNS, even with the present limitations.

We recommend that in the future, if data becomes available, to properly analyse the Cost-Benefit of the HPV vaccination programme on the prevention of all related cancers and precancerous lesions associated to HPV, to conclude if exists a real Cost-Benefit, already considering the most recent alterations to the HPV vaccination programme.

Acknowledgements

I am deeply thankful to Professor Victor Rodrigues and Dr. António Queimadela for all the support and availability throughout all these months, helping me overcome the obstacles that appeared during the realization of this thesis.

I also want to thank all Public Health Doctors who inspired me to make this thesis a reality.

I must thank my family, especially my mother, for all the support and patience given throughout this process.

Finally, I want to thank my boyfriend and all my friends, they made me enjoy the small things in life during this journey.

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