Facultad de Ciencias Económicas y Empresariales

TRABAJO FIN DE GRADO

GRADO EN ECONOMÍA

Economic evaluation of Varicella Vaccine

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EXECUTIVE SUMMARY:

Objective: The purpose of this research is to analyze the topic of health economics and more precisely understand the method of cost- effectiveness analysis of health technologies. The theoretical framework will be applied to the Varicella and the varicella vaccine, performing a cost-effectiveness analysis for the varicella vaccination strategy to children in Navarre.

Methods: A Markov model is designed to estimate costs of the strategy using no vaccination as comparator. Tree Age Data program software is used.

Results: The cost-effectiveness analysis done concludes that the program of vaccination will prevent 327 cases of Varicella. Additionally, the health system of Navarre will save, by applying the vaccination program, 352,903.376 Euros, what means that the vaccination is a dominant strategy compared with no vaccination.

KEY WORDS: Economic evaluation, Cost effectiveness, Varicella vaccination, Health Economics, Varicella in Navarra.

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1 INTRODUCTION

Economics deal with the allocation of scarce resources, thus, health economics is in charge of the resource allocation among different health treatments, programs and interventions. Governments around the world concern about the financing of health care and want to find an efficient allocation of means. In the light of limited funding, governments use economic evaluations of health interventions as a decision tool when considering a limited range of options within a given field.

The economic evaluation of health interventions is becoming increasingly important in the evaluation of the different treatments available for infectious diseases. A health economic evaluation can be performed following different types of analysis. The cost effectiveness analysis is commonly used in the evaluation of interventions of communicable diseases such as the Varicella vaccine.

Several studies around the world have assessed the effectiveness of the Varicella vaccine. These papers agree in the effectiveness of the Varicella vaccine in a range of 70% and 90% depending on the methodology used. However, the number of studies that deal with cost effectiveness analysis of the Varicella vaccine is low.

Varicella Zoster Virus (VZV) produces two clinical forms; the Varicella virus and the herpes zoster. In the absence of vaccination, the Varicella virus has an incidence almost equal to the birth rate. More than 90% of the population of 15 years aged had already suffered from Varicella virus, the virus is most common in children .Complications are rare however the virus in the adulthood is much more complicated. Once an individual has been infected with Varicella virus a life lasting immunity emerges. After the Varicella, the virus remains latent in the organism and can reactivate in the future as the Herpes Zoster. The Herpes Zoster is a more serious disease; the literature concludes that approximately 15% of the people that were infected by Varicella develop Herpes Zoster.

The Varicella vaccine, developed in 1995, consists of a subcutaneous administered dose of attenuated live virus. The vaccine was introduced for the first time in Navarre in 2004 for susceptible teenagers of 14 years old. It was not until 2007 when the Varicella vaccine was introduced in the systematic and free vaccination schedule. Nowadays, in Navarre it is a two dose vaccine at 15 months and three years aged. The rate of incidence of Varicella in Navarre has decreased by an 89% from 2006 to 2012.

An important phenomenon can occur with the Varicella vaccine, the Varicella breakthrough. This event is a vaccine failure that causes a vaccinated individual to suffer from a mild Varicella. The literature review of breakthrough Varicella points out that this happens in 15 to 25% of the cases.

Controversial points of view exist with respect to the Varicella vaccine. Supporters of the vaccine claim its effectiveness. On the contrary the group against Varicella vaccine holds up to the argument that Varicella vaccine can increase the presence of Herpes Zoster.

The main objective of this study is to evaluate whether the Varicella vaccine is cost-effective in Navarre from a health care´s perspective, taking into account only direct costs. The data used in this study is based in a previous study about the cost effectiveness of Varicella vaccine in Spain. This study made by Peña Rey, Pérez Farinós, Cortés García, & Amela Heras in 2004 studied the cost effectiveness of the varicella vaccine in Spain for a cohort of 13 years old in 2001. The result was that avoiding one case of varicella vaccine will cost the health system 131 euros.

The first part of the project deals with the subject of economic evaluations. It is followed by a detailed explanation of the Varicella and the Herpes Zoster viruses. In this section the epidemiology of the virus is explained as well as its effectiveness and incidence rates in the world and specifically in the autonomous community of Navarre. In relation with the previous section of the Varicella and Herpes Zoster the project follows with a section of the Varicella vaccine. A literature review of the researches made about the cost-effectiveness of the varicella vaccine has been made as well before going to the last part of the paper. The final aprt consists of a cost- effectiveness analysis of the varicella vaccine in Navarre.

2 OBJECTIVES AND METHODOLOGY

The purpose of this research is to analyze the topic of health economics and more precisely understand the method of cost- effectiveness analysis of a health treatment. As a real life example, a cost- effectiveness analysis of the Varicella vaccination in Navarre is going to be performed. The purpose is to evaluate whether the vaccine is cost- effective in the case of Navarre.

In order to do the analysis, the health costs involved in the two alternative health treatments (vaccination or no vaccination) have been obtained by contact with people from the health system and based in previous studies of the same topic in Spain.

The population data have been obtained from the ¨Instituto Nacional de Estadística¨ (INE). The Varicella incidence rates in Navarre were obtained from previous studies of the Varicella in Navarre and from the ¨Instituto de Estadística de Navarra¨.

The data of hospitalization, complications, Varicella and herpes zoster rates have been obtained from a cost- effectiveness study of the Varicella vaccine in Spain.

3 ECONOMIC EVALUATION OF HEALTH CARE

Economic evaluation of health care tries to give the value for money of the different health technologies and treatments. An economic evaluation makes a comparative analysis of the different courses of action in order to compare costs and results. Thus, economic evaluation of health care evaluates the costs of different health interventions and compares the results of those programs (Kobelt, 2013).

The final intention of a health economic evaluation is to choose the most appropriate alternative among the range of available options which maximizes health outcomes. Nevertheless, programs or treatments with better outcomes are usually associated with higher costs compared to those with lower outcomes, in those cases it is important to evaluate if the incremental benefits are worth the higher costs.

Inputs are defined as the costs of implementing the treatment minus the costs saved by the treatment for example the avoidance of a hospitalization. On the other hand outputs are defined as the benefits of the treatment in terms of a reduction in mortality, improved quality of life, patients cured and many more.

In economic evaluations there is a distinction between direct costs and indirect costs. Direct costs are the value of the resources used such as hospitalization, medicines etc.

However indirect costs are not directly accountable to the treatment but are important to take into account and sometimes the value of the indirect costs is high. These include the loss of productivity, the time spent by the family or the time spent by the patient.

3.1 Distinguishing features of economic evaluations

Economic evaluation of health programs is based on a comparative approach in which inputs and outputs of two or more programs are compared in order to choose the most efficient alternative. According to Drummond, et al , there are four main types of economic evaluations which differentiate between them in the method used to value and quantify outcomes; cost minimization analysis, cost- benefit analysis, cost effectiveness analysis and cost-utility analysis. The choice of method of analysis must be made with accordance to the research question that is pretended to study.

3.1.1 Cost minimization analysis

Programs which are equivalent in health outcomes are evaluated through a cost minimization analysis (CMA). The CMA evaluates two or more therapeutic alternatives with the same effectiveness and compares the monetary costs of these alternatives. The equivalence between the different treatments must be proven and presented in a comprehensive way. When two alternative treatments or programs conduct to the same health results then the less costly option is preferred.

The implementation of the cost minimization analysis is rare since it requires outcomes of the programs to be equal. Usually treatments differ in costs but also in effectiveness. New treatments or programs came with higher costs but provide better results as well. In those cases other types of analysis have to be made in order to evaluate whether the increase in output overweight the incremental costs.

The advantages of the CMA are that it is easy to use and results are found quickly. However the drawbacks of CMA are mainly three; the treatments compared have to have equal effectiveness, this type of analysis does not inform if costs exceed or not the monetary value of the effects and it does not allow to make comparisons among programs of different nature.

3.1.2 Cost- Benefit analysis

The cost benefit analysis (CBA) accounts not only inputs but also outputs in monetary terms. The CBA values all health results in monetary terms against all costs of the treatment or program. The benefits of the programs are defined in CBA as the maximum willingness to pay of individuals for that intervention. CBA compares programs or treatments with single or multiple effects that are not necessarily common to the different alternatives.

The main strength of a cost benefit analysis is that it allows comparison between every type of alternative. That is why it is commonly used when significant amounts of money are considered.

On the other hand, in CBA to monitor all effects and most of the times the intangible effects are not taken into account. Additionally, in practice it is difficult to assess monetary values to health results.

The methodology in this type of analysis is simple; a discounted net value or a ratio between costs and benefits is usually made. As said, the difficulty resides in the valuation of benefits.

3.1.3 Cost- Effectiveness analysis

The cost effectiveness analysis (CEA) expresses costs in monetary units and the outcomes in non-monetary units. The effectiveness is measured in terms of natural units, such as years of life gained, hospital days prevented, patients cured, reduction in clinical parameters and others. The programs and treatments compared by this type of analysis have single effects that are common to all the alternatives but are achieved at different degrees.

The cost effectiveness analysis can be used for several treatments or programs, for instance it is widely used to make economic evaluation of infection disease programs such as vaccines.

CEA allows the valuation of intermediate results and the comparison between alternatives of different natures as long as they have results expressed in the same units such as hospitalizations avoided, infections avoided and others. This can be seen as well as a drawback since it does not allow decision makers to compare interventions that have different results. Additionally it does not give information of whether the results exceed or not costs.

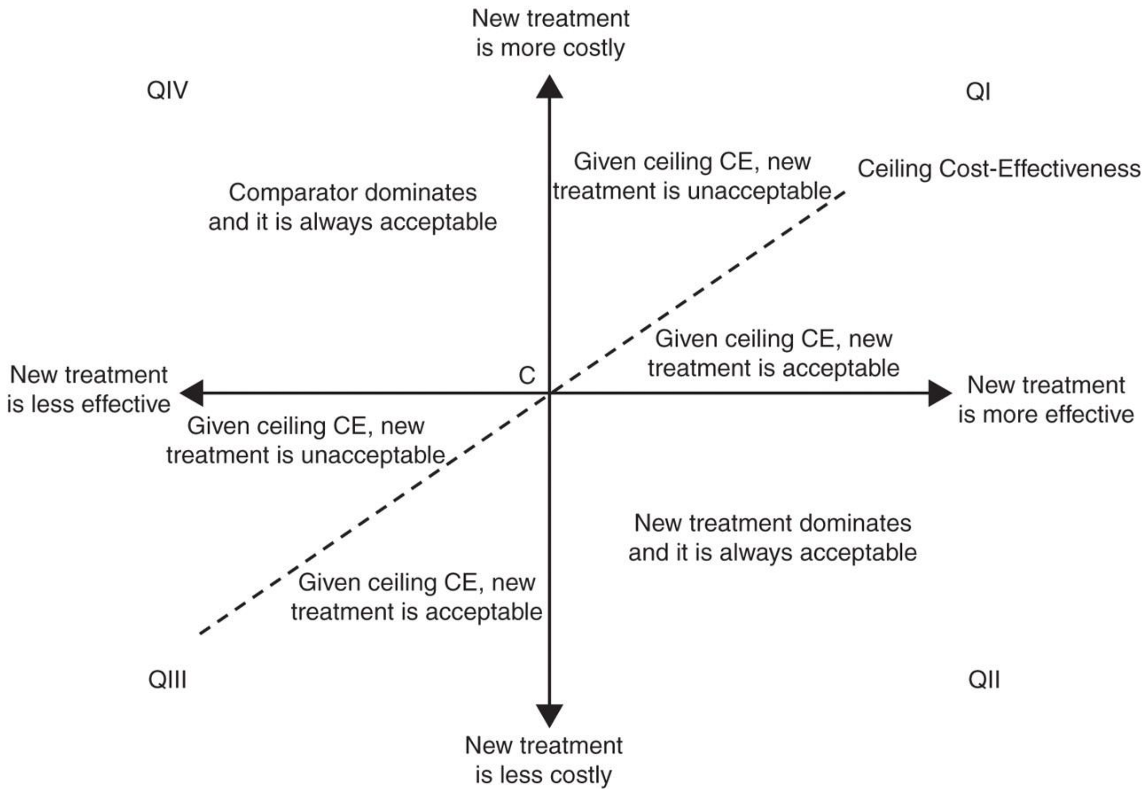
A mathematical relation is used in order to find the cost effectiveness measure. The Incremental Cost Effectiveness Ratio (ICER) is commonly used.

$$ICER = \frac{C1 - C0}{E1 - E0}$$

This mathematical expression divides the difference in costs of the alternative and the comparator treatments between the difference in effectiveness of the treatments. If life-year gained is the effectiveness measure then the ICER will be interpreted as the incremental cost per unit of life-year gained.

Figure 1 represents an incremental cost- effectiveness plane. This figure is divided in four quadrants and it helps decision makers to understand which alternative to choose. The vertical axis represents the cost difference between the intervention and the alternative (C) and the horizontal axis represents the effectiveness difference between the intervention and the alternative (C).

Figure 1. The cost- effectiveness plane



Source: Maniadakis, N., Vardas, P., Mantovani, L. G., Fattore, G., & Boriani, G. (2011). Economic evaluation in cardiology. *European Society of Cardiology* , ii3-ii8.

The ICER points situated in quadrants QII and QIV are easy to interpret. In quadrant QIV the intervention is less effective and more costly than the alternative, thus, this treatment is not desirable and will be thrown out, and hence, it is a dominated intervention. In quadrant QII the intervention is more effective and less costly so this alternative is clearly more desirable than the alternative, it is a dominant intervention.

On the other hand, the results in quadrants QI and QIII the decision is not straightforward. In quadrant QI the treatment or intervention is more effective and more costly than the alternative. However, in quadrant QIII the treatment is less effective and less costly than the alternative. If ICER is situated in any of the two quadrants the decision will have to be evaluated if either the increased costs are worth the more effective intervention or if the less effective but less costly intervention is preferred.

The ceiling cost-effectiveness (CE) divides each QI and QIII in two sections. It can be interpreted as a reference ICER. If the ICER is in the left side of QI above the CE the treatment is unacceptable since it is more costly and less effective than the reference point. However if t is in the right hand side below the CE the treatment is acceptable because the treatment is more effective and less costly than the reference. Same happens in QIII; if ICER is in the left above the line the treatment is unacceptable, if it is in the right below the line then the intervention is acceptable. To draw the ceiling line, a monetary value to the unit of effectiveness has to be assigned.

3.1.4 Cost- Utility analysis

The cost utility analysis (CUA) is a type of cost effectiveness analysis which measures the costs in monetary units but measures outcomes in utility units instead of natural units. The CUA measures health results in utility adjusted units such as the quality adjusted life year which is the most commonly used result measurement. This concept measures life expectancy adjusted with the quality of life. Cost utility analysis is commonly used to evaluate treatments or programs in which the quality of life is an important aspect of the therapy.

The results obtained in this method can change depending on the method used due to the absence of a well-defined methodology. However, CUA has an important advantage; it allows the decision maker to compare different type of alternatives with health as outcome, irrespective of the particular illness studied, and to integrate the quantity and quality of life of the patients which is considered really important by the health system.

3.2 How to choose the type of economic evaluation?

The decision of the type of economic evaluation is not random and some steps should be followed in the decision. In order to perform an economic evaluation of a health intervention, the first question that has to be assessed is if there is evidence of the effectiveness of the program. If the program is not effective it makes no sense to make an economic evaluation but it will be convenient to perform a cost analysis. If the program is effective another question emerge; is the effectiveness of the programs equal?

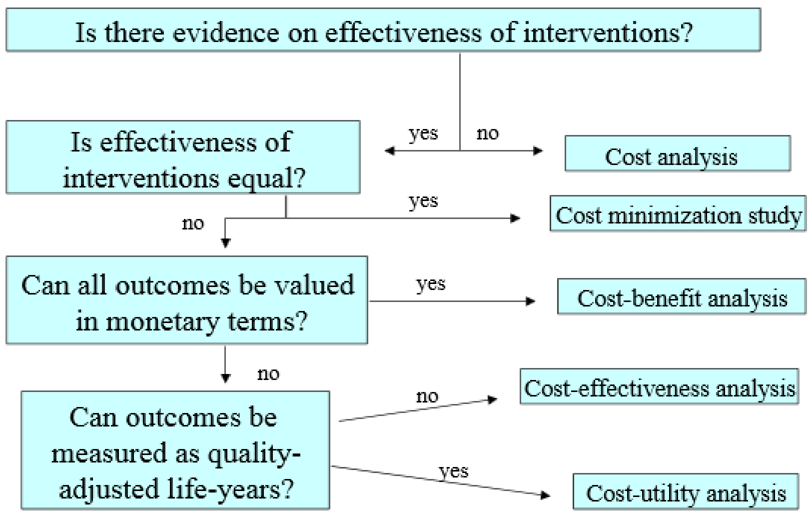
If the effectiveness of the interventions is equal then a cost effectiveness analysis has to be performed. However, if the effectiveness is not equal the third question emerges; can all outcomes be valued in monetary terms?

A cost- benefit analysis can be made if the outcomes can be valued in monetary terms. If outcomes cannot be valued in monetary terms then the last question has to be asked; can outcomes be measured as quality- adjusted life- years?

If QALYs cannot be obtained then cost- effectiveness analysis is the most appropriate measure with an incremental cost effectiveness ratio. However, if QALYs can be obtained then a cost-utility analysis can be convenient.

Figure 2 represents the process explained above with the questions and the types of economic evaluations.

Figure 2. Types of economic evaluation



Source: Gray, A., Davies, P., Mant, J., See, K., & Snowball, R. (1999). *Economic Evaluation. Evidence-Based practice:A Primer for Health Care.*London.

3.3 Impact of economic evaluations on health care decisions

The economic evaluation of heath decisions has gained through the last few years an increasing importance. Public institutions, health care managers and researchers in the field of health economics recognize the value of economic evaluations in the decision making inside the health care system. However, still nowadays, few health procedures or treatments are evaluated.

England is one of the countries with the higher use of economic evaluations to face health decision. The National Health Service is the publicly funded health care system in England and is in charge of all the treatments and programs evaluations among other activities. As a consequence, England is the country of reference when assessing the impact that economic evaluations have in the decisions made with respect to health matters.

The studies made about the importance given by decision makers to the economic evaluations of health care show that decision makers do recognize the usefulness and the need behind economic evaluations of health care. However, due to the narrowness of the research question, the difficulty to generalize the results and the lack of methodological rigor is most of the times difficult and impractical to apply the results of the evaluations. Most of the decision makers recognize the importance of economic evaluations but claim for methodological improvements in order to increase the reliability of the results. (Hoffmann et al, 2002).

The difficulties of implementing the results of the economic evaluations of health care have been assesed and classified in an study of Oliva et al, in 2006. They refer to this problems as barriers of economic evaluations and they made a classification in three groups; administrative barriers, methodological barriers and practical barriers. The first type of barriers is related with the rigidity of the administrative structure of the health system, in here it is named the difficulty of passing from one budget chapter to another. The methodological barriers refer to the lack of a proper hypothesis or the low standarization of the method. Finally the third type of barrier refers to lack of reliable resources in order to make economic evaluations, for instance the lack of a reliable unit cost for a day in the hospital, or the cost of administrating a vaccine.

Both studies conclude that people in charge of making health decisions are aware of the importance of these evaluations. Nevertheless improvements in the methods and resources used are needed in order to be able to apply the outcomes to the real life and base a health decision on those results.

4 VARICELLA ZOSTER VIRUS

4.1 Epidemiology

The Varicella Zoster Virus (VZV) produces two clinical forms, the Varicella or chicken pox and the herpes zoster or shingles. The VZV is a member of the herpes virus and like other viruses in this group it has the ability to persist as a latent infection in the sensory nerve ganglia after the first infection.

The virus enters the body through the respiratory tract and then it disseminates to other organs such as the liver, spleen and sensory ganglia. The Varicella Zoster Virus has an incubation period of 14 to 16 days, although it may be prolonged from 10 to 21 days in some cases.

Varicella and Herpes Zoster is a human disease that can be found in a worldwide geographic distribution. However, the virus is more prevalent in temperate climates countries in which around 90% of the population has Varicella before 15 years age (Whitley, 1997). In these temperate areas the Varicella has seasonal fluctuations with peaks occurring in winter and spring. For instance, in the United States the incidence is higher in March and May than in September or November.

Every individual that has not suffered from Varicella or has not been vaccinated is susceptible to Varicella virus. In the absence of vaccination, the annual incidence rate of the Varicella virus is almost equivalent to the birth rate.

Varicella Zoster Virus is a highly contagious infection and the transmission of VZV mostly occurs by contact of a healthy individual with an infected one by the inhalation of infected respiratory tract secretions. However it can also be transmitted by vesicular fluid of skin lesions of acute Varicella or Herpes Zoster.

Infected patients of Varicella Zoster Virus are contagious from one to two days before the onset of the rash until lesions have formed crusts (usually five days), after this moment the probability of being infected by these sick patient decreases. Varicella attacks among susceptible household contact is approximately 90%, the probability of being infected by contact with an immunocompromised individual is thus really high.

4.2 Primary infection or Chickenpox

The Varicella (chicken pox) is a highly contagious disease that results in a skin rush with small blisters that primarily involves the trunk and face. The symptoms usually last five to ten days and can include, skin rush, fever, tiredness and headaches. In some rare occasions the primary Varicella can lead to more severe disease and visceral invasion. In temperate climate countries Patients that have suffered from Varicella virus acquire a life lasting immunity, which is one of the main characteristics of the virus.

The primary infection of the Varicella zoster virus is common amount children, several studies conclude that, in temperate climate areas, by the age of 15 years 90% of the population has been infected from chickenpox and 95% of the population is infected before adulthood. It is rare in adults however the fatality of the cases increase in the adulthood.

Even though, most people who suffer from Varicella recover without problems, around 2 to 6% of the cases present complications. Complications can be virally mediated; neurological, pulmonary, hemorrhagic and congenital infection. Additionally complications can be bacterially mediated; pneumonia, sepsis and skin and soft tissue. These complications are more common at extremes of age, in patients with cellular immune deficiencies or pregnant women. Nevertheless, most acute complications and deaths occur in healthy patients.

4.3 Recurrent disease or Herpes Zoster

In later life, after the patient has suffered from Varicella, the virus can reactivate in the form of the herpes zoster virus which usually appears in the adulthood and it tends to be more severe with age. Several studies proved that more than half of the cases of Herpes Zoster occur in adult individuals. However it can occur in children as well but it is almost painless, on the contrary for adults it is more complicated and dangerous than the Varicella in children.

The herpes zoster is not a seasonal virus and the incidence has the same probability among all seasons. The rates of reactivation of the Varicella in form of Herpes Zoster infection have been around 15% of the people who suffered from Varicella. (Peña-Rey Lorenzo, et al , 2004).

The symptons are similar to the chickenpox with headaches, fever and malaise. These ones are followed by sensations of pain, itching, hyperesthesia or pareesthesia.

The virus usually spreads from one or more ganglia to nerves connecting to it, causing a painful rash. This rash usually heals in between two or three weeks. However there are cases in which the residual nerve pain stays even for years, this condition is called postherpetic neuralgia.

5 VARICELLA VACCINE

In order to reduce the infection of Varicella, a vaccine against Varicella virus was developed in 1995. This vaccine is marketed as Varivax in the United States and as Varilrix globally.

The Varicella vaccine consists of a subcutaneous administered dose of attenuated live virus meant to protect against the viral disease of chicken pox. A two dose vaccine is universally recommended. The first dose is usually recommended at 12 to 15 months and the second dose at 4 to 6 years of age.

Inside Europe, Varicella vaccine for children is recommended universally at a national level in only six countries; Germany, Latvia, Greece, Cyprus, Luxemburg and Austria. At regional level only two countries (Spain and Italy) recommended the vaccine. Other 16 countries in Europe recommend vaccination nationally for susceptible teenagers and groups of people under risk conditions.

The effectiveness of the Varicella vaccine has been studied by diverse authors and in different countries and most of these studies conclude that the vaccine is effective in 70% to 90% of the cases.

There are controversial opinions about whether the vaccine is a good idea. The vaccine introduces weakened live Varicella Zoster Virus to the organism so it can contribute to the reactivation of the virus in the form of Herpes Zoster in the future. Shingles cases may increase after the introduction of the vaccine but there is still no study that proves so. Nevertheless, the risk of developing herpes zoster after vaccination is less than the risk due to natural infection resulting in chickenpox.

Side effects of the vaccine are rare but can occur. For instance, some children who are vaccinated present a fever or a mild rush. These side effects can include redness, soreness at the injection point and stiffness.

Another vaccine was also developed for the Herpes Zoster virus, called Herpes Zoster vaccine. The only difference is that the dose of the vaccine for the Herpes Zoster is a larger than normal dose of Varivax.

5.1 Varicella breakthrough

The Varicella breakthrough occurs in people that were already vaccinated, it can be considered as a vaccination failure. It is defined as wild type of Varicella that occurs in vaccinated individuals. According to a cost effectiveness analysis of the Varicella vaccine in Spanish adolescents, the vaccine is effective partially in a 24% of the cases that develop Varicella breakthrough which is a milder version o the Varicella. (Peña Rey, et al , 2004)

The symptoms are the same but much milder than those of the normal Varicella and usually these last fewer days. For instance, individuals who present breakthrough Varicella usually have less than 50 skin lesions whereas the normal Varicella causes between 200 and 400 vesicles.

Two factors are considered as risk factors however not enough evidence exists in order to confirm and prove them. For instance, the vaccination at a younger age may be a reason of vaccine failure. Increasing time since the immunization may be another risk factor. Nevertheless no conclusive evidence is available for these risk factors.

5.2 Herd immunity

One important phenomenon that happens with Varicella vaccination is the herd immunity. Herd immunity happens when a significant percentage of the population are immune to a contagious disease.

Once a certain percentage of population is immune to the virus, in this case the Varicella, the rest of the population acquires an indirect immunization. The chains of infection are likely to be interrupted when large amount of the population are immune.

The greater the proportion of vaccinated individuals the greater is the herd immunity effect and the probability that a susceptible individual will come into contact with an infected individual decreases.

Taking into account this effect can be interesting in economic evaluations from a social perspective. If only a certain percentage of the population is vaccinated an almost complete coverage could be found and this has some monetary repercussions for the society that could improve the economic effectiveness of the Varicella vaccine. However, most of the cost- effectiveness studies do not take into account this effect since it is difficult to monitor and to assess a monetary value.

This effect has decreased the incidence of chickenpox in adults; however, it has increased the prevalence of shingles which is a more critical condition.

5.3 Vaccination strategies

There are two types of vaccination strategies that can be applied by a health system; vaccination to high risk individuals or universal vaccination.

The strategy of high risk strategy consists of vaccinating specific groups of the population considered to have higher risk of complications than the rest. The priority groups defined by García Cenoz M. in 2014 are the following:

- Immunocompromised children and their families.
- Health personnel
- Women in childbearing age before pregnancy
- Schools personnel
- Teenagers and susceptible adults

The strategy of universal vaccination consists in the introduction of the Varicella vaccine to the systematic and free vaccination schedule. The World Health Organization recommends the adoption of the universal Varicella vaccination since it has been proven the reduction in the incidence of the virus as well as the decline in complications.

6 VARICELLA AND VARICELLA VACCINE IN NAVARRE

6.1 Varicella incidence before and after the introduction of the Varicella vaccine in the immunization schedule of Navarre

The Varicella vaccine was introduced for the first time in the systematic immunization schedule of Navarre in 2004 for susceptible teenagers of 14 years old. In 2006 the vaccination was advanced four years and it was set at 10 years of age. Additionally in 2006 a vaccine campaign was made in schools in order to vaccinate susceptible individuals born in 1992 and 1995.

Finally, in 2007 the systematic and free vaccination was introduced. Since the last modification and the introduction in the vaccination schedule the vaccine consists of two doses, with the first one at 15 months age and the second at 3 years of age. A vaccination campaign was made at three years age for the individuals born in 2004 and 2005 and the vaccine was kept at 10 years aged for the cohorts born before 2004.

Figure 3 shows the immunization schedule of Navarre of year 2014. The first dose of Varicella vaccine is at 15 months aged and the second dose, which is administered together with the rubella vaccine, is set at 3 years aged.

Figure 3. Immunization schedule of Navarre in year 2014.

CALENDARIO 2014										
VACUNAS	EDAD									
	2 MESES	4 MESES	6 MESES	12 MESES	15 MESES	18 MESES	3 AÑOS	6 AÑOS	12/13 AÑOS	14 AÑOS
Poliomielitis	VPI	VPI	VPI			VPI				
Difteria-Tétanos-Pertussis	DTPa	DTPa	DTPa			DTPa		dTpa		Td[7]
Haemophilus influenzae b	Hib	Hib	Hib			Hib				
Hepatitis B	HB[1]	HB	HB			HB[4]				
Enfermedad Meningocócica C		McC[2]		McC					McC[5]	
Sarampión-Rubéola-Parotiditis				TV[3]			TV			
Varicela					V		V			
Virus del Papiloma Humano									VPH[6]	

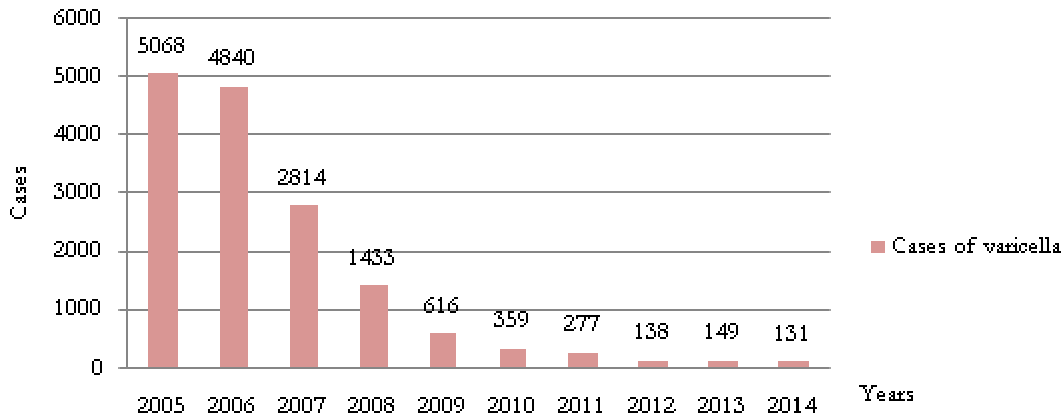
Source: Instituto de Salud Pública y Laboral de Navarra

The Institute of Public Health of Navarra periodically presents informs about the situation of notifiable diseases in Navarre. Varicella virus is included in the group of notifiable diseases in the autonomous community of Navarre and so the data of the number of cases of Varicella is presented in those informs.

Graph 1 represents the cases of Varicella vaccine in the period of 2005-2014. It can be seen that before the introduction of the Varicella vaccine the cases of Varicella were around 5000 each year. The peaks of the Varicella virus were in winter and spring, where there is a higher concentration of Varicella cases than in the rest of the seasons. According to the CMBD (Conjunto Mínimo Básico de Datos de alta hospitalaria), in the years 2005 and 2006 there were 80 hospitalizations in Navarre and the major complications were pneumonia and encephalitis.

Right after the introduction of the vaccine there was a decrease of a 40% in the number of cases affected by Varicella virus from 2006 to 2007. Overall the introduction of the vaccine has caused a sharp decrease in its incidence from levels of 5000 each year to levels of 131 cases in 2014. The 95% decrease in the number of patients affected by Varicella virus supports the hypothesis that the vaccine helped to prevent and decrease the cases of Varicella virus in Navarre.

Graph 1. Cases of Varicella virus in Navarre in the period 2005-2014

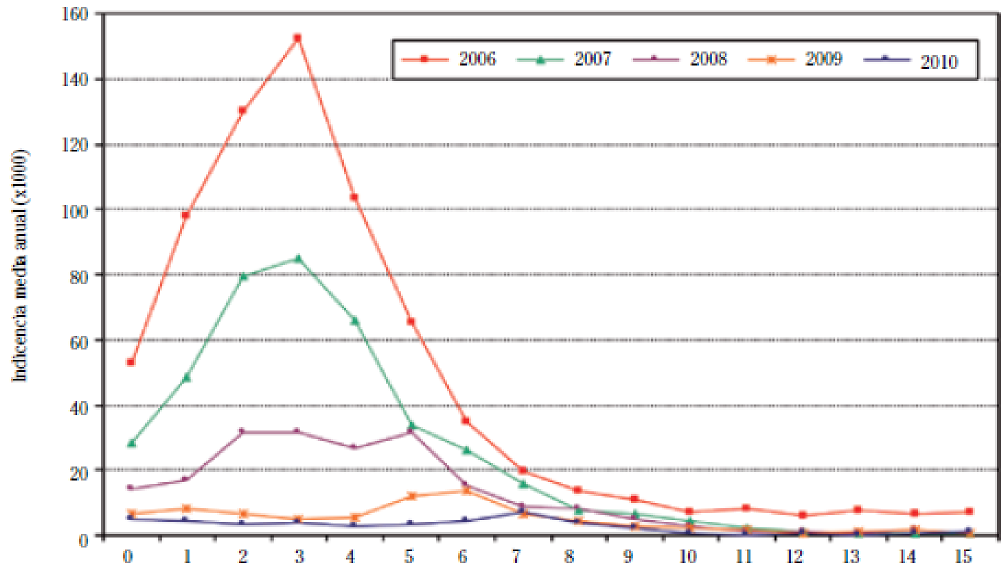


Soruce: Own elaboration base on the data of the ¨Boletín de Salud Pública de Navarra¨ (Febrero 2015 nº8)

According to the study made by García Cenoz M. et al (2008) about the incidence of Varicella virus before the introduction of the vaccine, the Varicella virus has proven to affect more in the range of age before 10-14 years old. This paper concludes that the maximum incidence of the virus was at age group of 0 to 4 years. By the age of 15 years old, 90% of the population had already suffered from Varicella virus. The year right after the introduction of the vaccine, 2006, the incidence of the Varicella virus in Navarra was an 18% lower than the median of the previous five years.

In graph 2 it can be seen the annual incidence of the vaccine per age group. In the study of García Cenoz et al (2011) has been noticed that the incidence of the Varicella has been delayed after the introduction of the vaccine. In 2006, 89.2% of the cases happened before 15 years aged whereas in 2010, only 76.6% of the cases were diagnosed.

Graph 2. Annual incidence of Varicella per 1000 inhabitants in less than 15 years aged individuals for the period 2006-2010 in Navarre.



Source:García Cenoz, M., Castilla, J., Irisarri, F., Arriazu, M., & Barricarte, A. (2011). Impacto de la vacunación universal frente a la varicela en Navarra, 2006-2010. *Anales del Sistema Sanitario Navarro*, 193-202.

A recent study made by the same authors evaluates the number of hospitalizations and complications of the Varicella in Navarre (García Cenoz, y otros, 2012). The incidence rate of Varicella in Navarre declined by 89% from 2006 to 2012. Additionally, the cases of complications from Varicella decreased from 10 cases in 2006 to none in 2012. The mortality rates due to Varicella are very low worldwide and the same happens in Navarre with only two cases in the period 2006-2012. The vaccine has helped to reduce not just the incidence of the virus but also to decrease the complications and hospitalization due to Varicella.

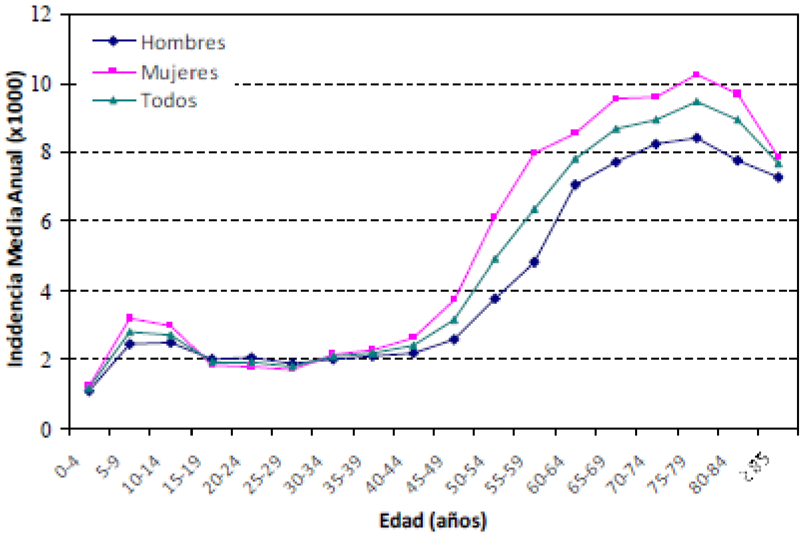
The vaccination failures or Varicella breakthrough appeared in 0.56% of the vaccinated children in the period of 2007-2013. After the first dose 39.6% of the vaccine failures happened and 30.6% of the Varicella breakthroughs took place in the second year after the administration of the second dose. Only 4% of the vaccination failures happened after the third year. (García Cenoz M. , 2014)

6.2 Variations in the incidence rates of the Herpes Zoster with the introduction of the Varicella vaccine in Navarre.

The incidence of herpes zoster increases with age, being the range of age of 75-79 years old the highest in incidence rates.

The incidence of herpes zoster among different age groups in the period of 2006-2012 in Navarre can be seen in graph 3.

Graph 3. Annual average incidence rate of Herpes Zoster in Navarre by age groups and gender in the period 2006-2012.



Source: García Cenoz, M. (2014). *Impacto y efectividad de un programa de vacunación infantil frente a la varicela, con dos dosis, en Navarra, 2006-2012.* Pamplona: Universidad de Navarra.

As can be seen the incidence rates increase sharply since 40-44 years old with the highest incidence in the range of 75-79 years old. After that range of age, the incidence of herpes zoster decreases but it remains high.

It can be seen in the graph that the incidence of herpes zoster is higher in women than in men and the difference increases from 40 years aged onwards.

After the introduction of the Varicella vaccine, several changes were noticed with respect to the incidence rates by age group. (García Cenoz M. , 2014)

- Increase of a 16.6% in the incidence of HZ in people aged between 70 to 79 years.
- Decrease of a 27.6% of the incidence of HZ in population aged less than 20 years.
- Decrease of a21.2% in the incidence of HZ in the age group of 50-59 years old.

The rest of age groups did not experience a significant change in the incidence rates of the herpes zoster after the introduction of the Varicella vaccine. The overall result found in the paper by García Cenoz M. in 2014 with respect to the influence of the varicella vaccine in the incidence of herpes zoster in Navarre is that the overall changes were not significant to extract conclusions.

7 LITERATURE REVIEW: COST EFFECTIVENESS OF VARICELA VACCINE

A wide range of studies around different countries, such as the United States, Canada or Spain, have assessed the study of the effects of the Varicella Vaccine. Some of these researches performed a cost-effectiveness analysis of the vaccine in order to evaluate the results and give a conclusion about whether the vaccine is cost effective or not.

The advantages of using the cost effectiveness analysis is that the output is measured in natural units, so it is more reliable than in other cost analysis in which the outcome has to be translated to monetary terms. The inputs used can vary depending on the perspective of the analysis. If the study considers the society´s perspective, the health system´s perspective or just the patient´s perspective the costs involved are different. For instance one cost that is included in the society´s perspective and not in the rest is the productivity loss due to the disease, either by the family or by the patient itself. Additionally, two different analyses can emerge depending on whether the value of the herd immunity effect is included. When herd immunity is included the analysis is called dynamic and static analysis otherwise.

Herd immunity effect refers to the indirect immunity phenomenon that happens when a certain percentage of the population has become immune to an infection. This percentage of immunization provides an indirect measure of protection for individuals who are not immune. As it is expected, the larger the number of people that is immune, the lower is the probability for the non-immune people to suffer the disease. Thus, in the case of Varicella, the herd immunity effect can make a difference in an analysis but it is very difficult to account for it. As a consequence, most of the cost-effectiveness studies of the Varicella vaccine are static analyses which do not include the herd effect.

Finally it is important to consider as well that as it has been explained in previous paragraphs that costs are grouped into direct and indirect. The vaccines or other health treatments can divide direct costs into medical and non- medical. Inside the medical costs it is common sense to know that are the hospitalization, resources, tests, patient visits and other costs. The non- medical costs include the time spent by the family taking care of the patient, the transportation costs and other services used. Sometimes those costs are not taken into account in cost analysis but are a relevant cost source.

7.1 Cost-effectiveness analysis of Varicella Vaccine worldwide.

In here, the cost-effectiveness analysis of countries such as the United States, Germany, Canada, Australia and Spain are going to be presented as a literature review. It will help to contextualize the topic and contrast the results of our analysis with those found in these papers. The time horizon used by all the papers analyzed in this section is 30 years.

7.1.1 Cost-effectiveness in the U.S.A.

There is a lot of literature in the topic of effectiveness of the Varicella vaccine in the United States. Overall these studies conclude that Varicella vaccine effectiveness is in between 80.7% for the prevention of Varicella in general, 96.1% in the case of a moderate Varicella and 100% for the prevention of severe Varicella. (Seward, Marin, & Vázquez, 2008). However, not so many studies have been performed assessing a cost effectiveness analysis of the Varicella virus.

The research of Lieu, et al., 1994, examined a varicella vaccination program in the United States using a decision tree. The two alternative ways of action to perform the comparative in the analysis were the vaccination and the absence of vaccination. The results were the following: provided that the coverage of the vaccine was a rate of 97 %, the program would save more than 5 dollars for every dollar invested in the vaccination. This result was from a society´s perspective so the non-medical costs were included. However, from the health systems perspective the program will cost 2 dollars per case prevented or 2500 dollars per live saved.

An important aspect of cost effectiveness evaluations emerge here. The different perspectives of making the analysis do make a relevant difference. In the study of this authors the same vaccination program can be cost effective or not depending on the perspective taken. The program is effective if non- medical costs are included,i.e. if the social perspective is taken, whereas, the program is not cost- effective if the health care´s perspective is taken.

7.1.2 Cost effectiveness in Australia.

The paper of Schuffham, Lowin, & Burgess,(1999) makes a cost- effectiveness analysis of three different varicella vaccine programs and compares them with the alternative of no vaccination. The study takes to cohort of 12 months old and 12 years old. The first cohort is called infants and the second adolescents. Only direct costs were considered.

The first program is to vaccinate all infants, the second programs is to vaccinate adolescents that did not have varicella before and the third is to vaccinate all infants and to catch up for adolescents that did not have the varicella virus the first 11 years.

The results found in this paper were that the most cost- effective program was the one that vaccinated all infants. The ratios were that this programs could avoid 4.4 million cases, 13500 hospitalisations and 30 deaths over a 30 year period. The average cost of the program per case avoided was 64 dollars.

The main conclusion is that since a health´s care perspective is taken even the most cost-effective program is costly for the system and does not save money. However, probably if a social perspective would have been taken, the program could have save money to the system since the social costs are of great amount.

7.1.3 Cost- effectiveness in Canada.

In the case of Canada, Brisson & Edmunds, 2001, run a study of three different vaccination programs comparing them in cost- effectiveness terms with the no vaccination alternative.

The results found that from the health system´ s perspective varicella vaccination will cost 45,000, 51,000, and 18,000 dollars per life- year gained for the programs of infant, the catch-up campaing and a mix of the two. As with the rest of the studies, the cost-effectiveness of the programs improve if the social cost are taken into account. However, in this case the relationship with the Herpes Zoster was studied and they find out that the program was inefficient if the incidence of zoster was taken into account, 118000 dollars per life- year gained.

7.1.4 Cost effectiveness in Germany.

The cost effectiveness analysis for the case of Germany was followed by Banz, et al. in 2002. As the studies done in Canada and Australia there were three types of programs compared with the no vaccination alternative; universal vaccination at 15 months old, vaccination of susceptible adolescents and a mixed strategy of the two. The children vaccination program, from a health system´s perspective was the most cost- effective with 611,000 cases prevented and 4,700 complications prevented per year. Additionally they studied the same from a social perspective and the result was that the program could save approximately 51.3 million dollars per year.

The results of all this literature do support the previous argument that cost- effectiveness analysis of varicella vaccination programs result in cost saving outcomes if the social perspective is taken, otherwise the results imply a cost for the government.

7.2 Cost-effectiveness analysis of Varicella Vaccine in Spain.

The study of Peña-Rey Lorenzo, et al, done in 2004, develops a cost-effectiveness analysis of the varicella vaccine for Spanish adolescents. This paper will be used as a reference and part of the data will be taken to do the cost-effectiveness analysis of the varicella vaccine in Navarre in the next section.

The authors performed a cost- effectiveness analysis with two strategies; vaccination or no vaccination. As in most of the cases studied in this paper, a decision tree was built in order to compare the effectiveness of two alternatives; vaccination and no vaccination. The authors used a cohort of people aged 13 years in 2001.

The probabilities of the decision tree were calculated using the Bayer´s theorem with data of previous studies in the United States of America.

Only direct costs were considered in this study and those were taken from costs information of 1999. However the costs had to be expressed in 2002 terms so a correction factor of 1.068 was used. The cost of the vaccine was 34 Euros and the administration costs were 5 Euros and the discounted costs were calculated. The vaccination program was based in a two dose vaccination so the total cost was 78 Euros per person. Considering only direct costs from a health system´s perspective the results found in this paper were that the Varicella vaccine could prevent 27,278 cases of Varicella and preventing each case will cost the Health System of Spain 131 Euros.

8 COST-EFFECTIVENESS FOR THE VARICELLA VACCINE IN NAVARRA

An increasing number of studies of infectious diseases are implementing cost- effectiveness analysis.

For the case of Navarre, there is still no study that completes cost effectiveness analysis of the Varicella vaccine in Navarre. Nevertheless, for the case of Spain the previous mentioned study of Peña Rey et al, (2004) evaluates the cost effectivenes of varicella vaccine. As a result, this study will be used as a reference for the present section in which a cost-effectiveness evaluation of the varicella vaccine in Navarre will be performed.

8.1 Objective

The objective of this study is to perform a cost- effectiveness analysis of vaccinating a cohort of susceptible individuals that were 14 years old in 2001. The two alternatives used for this economic evaluation will be the strategy of vaccinating susceptible individuals against the alternative of no vaccination. A health system´s perspective will be used for the calculation of costs.

In order to make a cost-effectiveness analysis it is important to make sure first that the vaccine is effective. Several studies, as it has been explained in previous sections, prove that the vaccine is effective in a range between 70 and 95%. In this project a 71% effectiveness is used.

8.2 Data and methodology

A Markov model will be used in order to analyze the two strategies; vaccination or no vaccination. A Markov model is a stochastic model used to represent changing systems with different states. Markov models assume that future states depend exclusively from the present state.

The program Data TreeAge Pro has been used in order to design and obtain the results of the Markov Model.

The virus behaves in the same way in areas with similar characteristics, so it is reasonable to consider that in Navarre the virus behaves similarly to Spain. Is that way, the probabilities introduced in the model and the costs have been obtained partially from the study of Spain mentioned above.

The study has been performed using a cohort of 5,120 individuals that in 2001 were 14 years old. (INE), and using a health care´s perspective with a temporal horizon of 30 years.

In order to calculate the costs of the two branches of the tree a discount rate of 3% has been used. This discount rate is applied in order to take into account in the final costs the age in which each individual is going to get infected, with this, the temporal positive preference of the present against the future is considered. The formula applied is the following:

$$\frac{1}{(1+r)^t}$$

Being ¨r¨ the discount rate of 3% and ¨t¨ the temporal horizon in this case 30 years.

8.3 Costs involved

Only direct costs are considered in this cost-effectiveness analysis. Both strategies share the same type of costs; however the vaccination strategy has three additional costs.

Table 1. Costs of vaccination and no- vaccination strategies

	No Vaccination			Vaccination		
	Costs	Days/Doses	Total cost	Costs	Days/Doses	Total cost
Primary Care	17	1	17	17	1	17
Hospitalization varicella	243	7	1701	243	7	1701
Hospitalization Herpes Zoster	243	9	2187	243	9	2187
IgG	-	-	-	11	0,3	3,3
Vaccination	-	-	-	34	2	68
Vaccine administration cost	-	-	-	5	2	10

Table 1 summarizes the costs involved in the two alternative treatments purposed for the Varicella virus. Firstly, both strategies share the hospitalization and primary care costs. The average days spend in hospital due to Varicella has been observed to be 7 days, whereas in the case of Herpes Zoster, a patient stays an average of 9 days in hospital. As a consequence a hospitalization due to Varicella costs the health system 1701 Euros against the 2187 Euros that costs the hospitalization of a patient with Herpes Zoster. Primary care costs are 17 Euros and are shared by the two strategies.

On the other hand, vaccination strategy has additional costs related with the vaccine. The vaccine has a cost of 34 Euros, taking into account that in Navarre the Varicella vaccine is administered in two doses, the total cost of the vaccine will be 68 Euros. Additionally the administration costs are 5 Euros and with the same reasoning as the vaccine it has a total cost of 10 Euros. Summing up all costs related with the vaccine results in a total cost for the vaccine of 78 Euros. Finally, about 30% of the population does not know if they have suffered the Varicella virus. An IgG test is performed to those individuals in order to know whether they have had Varicella virus. This test is needed because Varicella vaccine has to be administered only to individuals who did not suffer from Varicella.

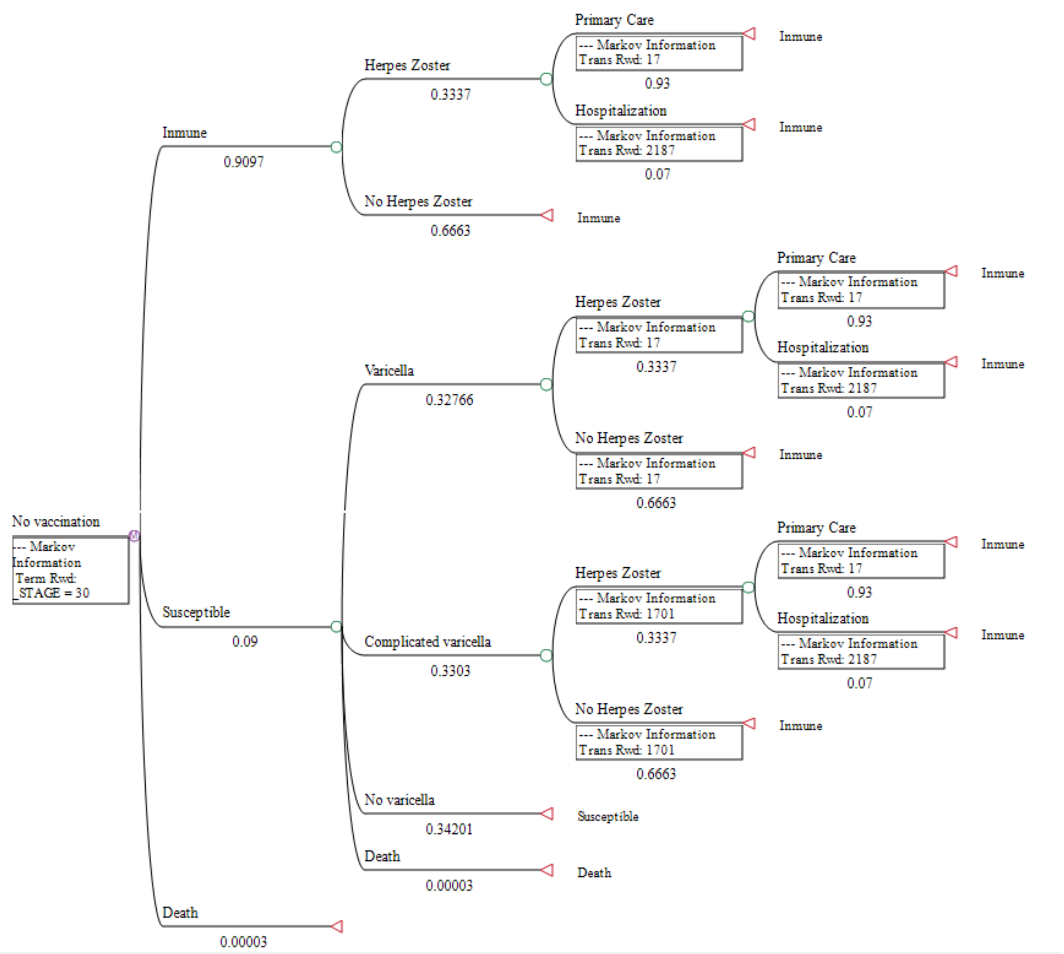
8.4 Markov model for the Varicella vaccine in Navarre

8.4.1 Transactional probabilities of the two strategies

Markov models represent the disease as a series of health states in which a patient can stay for a period of time. Markov models are widely used to analyze diseases with long time horizons, each time period is called cycle and the length of each cycle depends of the disease and the intervention being evaluated. The probability to go from one state to another is called transactional probability.

The model represented for the Varicella vaccine in Navarra is called Markov chain and the main characteristic is that the probability to go from one health state to another (transactional probability) remains constant during all the cycles.

Figure 4. Markov chain for the no vaccination strategy for Navarre



The Markov chain of the alternative of no vaccination can be seen in figure 4.

As it has been seen in the literature, by the age of 14 years, more than 90% of the population has suffered from Varicella. The first state is immune with a probability of 90%, in each cycle 33% of the immune individuals will have Herpes Zoster. Only 7% of the individuals with Herpes Zoster will need hospitalization.

The individuals who by the age of 14 did not suffer Varicella, 9% of the population aged 14, can go to 4 different health states. In each Markov cycle less than the 33% of the susceptible individuals will have Varicella, 33% will have complicated Varicella, 34% will not have Varicella and 0.03% will go to the absorbent state called death.

The final state is death with a probability of 0.03%, it is an absorbent state because the chain ends up and the individual that passes through that state cannot move to more cycles.

It is important to mention that every individual that in a cycle suffers Varicella or complicated Varicella will automatically go to the immune state in the next cycle. However, individuals who do not suffer will go again to susceptible state and finally people who go to the absorbent state will die.

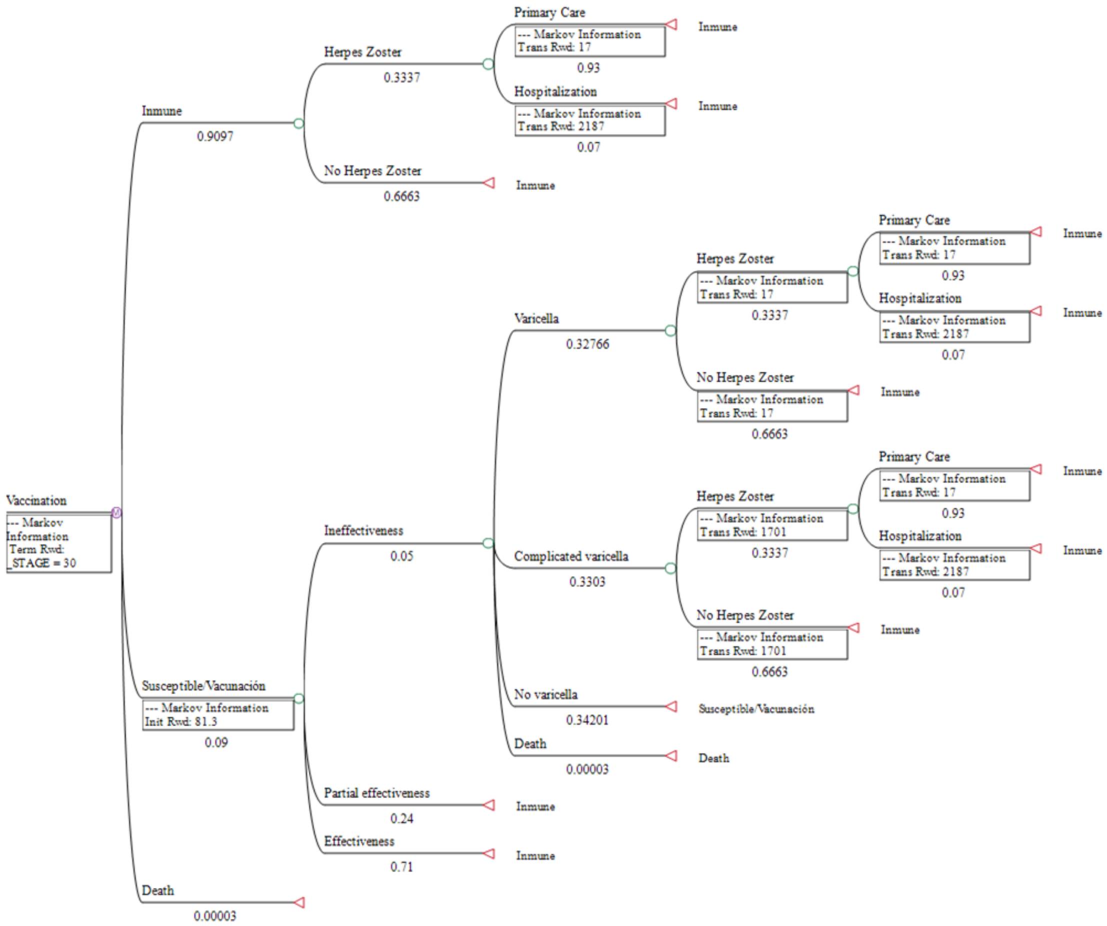
In figure 5 the Markov chain for the vaccination alternative can be seen. The first three states are the same as in the no vaccination strategy. However, in the susceptible state, three possible states emerge. The vaccine is in 71% of the cases effective, in 24% of the cases the vaccine is effective only partially and the individuals suffer what is called Varicella breakthrough, and only in 5% of the vaccinated individuals the vaccine is ineffective.

Individuals to whom the vaccine was ineffective can go through 4 states. In each cycle they can either have Varicella with a probability of less than 33%, complicated Varicella with a 33% probability, no Varicella with a 34% probability and death with a probability of 0.03%. As it happened with the no vaccination strategy, individuals who after Varicella suffer Herpes Zoster will have to be hospitalized with only a 7% probability.

Only individuals to whom the vaccine was ineffective and even though they did not suffer Varicella in one cycle, they will in the next cycle go to the susceptible state. The rest will go to the immune state or to the absorbent state.

The probabilities in the Markov chain are assumed to be the same in every cycle. In order to calculate the probability of Herpes Zoster, complicated Varicella and death an average of the conditional probabilities of those states for the different age groups has been performed. The conditional probabilities have been found in the paper of Peña Reyet al, 2004. Those probabilities can be found in Annex 1.

Figure 5. Markov chain for the vaccination of susceptible individuals of 14 years old in Navarre.



8.4.2 Payoff of the states of the two strategies.

One of the most important points of this economic evaluation of the Varicella vaccine in Navarre is the comparison of costs between both strategies; vaccination and no vaccination. In order to compare costs, the payoffs of each possible branch have to be introduced in the model.

Table 2 represents the payoff of each individual branch of the Markov chain. The first three branches of both strategies are the same. In branch one, the individual is immune but suffers from Herpes Zoster and is attended through primary care which has a cost of 17

Euros. The second branch is similar but the individual has to be hospitalized and so the cost is of 2187 Euros. The third branch is simple; the individual is immune and does not suffer Herpes Zoster so the cost is zero.

The only difference in the rest of the branches is that in the vaccine strategy it is added the cost of the vaccine and the cost of the IgG test, so the branches are 81.3 Euros more costly for the vaccination strategy. Additionally, the vaccination strategy has two more branches that represent the effectiveness or the partial effectiveness of the vaccine, for which the only cost is the vaccine cost and the IgG test cost.

The branches that emerge from the Varicella health state of the susceptible people have the cost of primary care plus additional cost if they suffer Herpes Zoster and have to be attended through primary care or hospitalization. Each susceptible individual that suffers Varicella is attended through primary care. In contrast each susceptible individual that suffers complicated Varicella is hospitalized and so all the branches that emerge from complicated Varicella will have a cost of 1701 Euros plus additional costs if they have Herpes Zoster as in the case of the Varicella cases commented before.

All the branches´ payoffs of both strategies result from adding up all the costs involved depending on the scenarios commented above. For instance, the branch where susceptible individuals that have complicated Varicella, suffer Herpes Zoster and have to be hospitalized has a cost of 3888 Euros. This results from the 1701 Euros of hospitalization due to complicated Varicella, plus the 2187 Euros of hospitalization due to Herpes Zoster. The same branch in the case of the vaccine has a payoff of 3969.3 Euros because in here it is included the 81.3 Euros of the vaccine and IgG tests cost.

Table2. Payoffs of the branches of the vaccination and the no vaccination strategies.

No vaccination		Vaccination	
Branch	Payoff	Branch	Payoff
1	17	1	17
2	2187	2	2187
3	0	3	0
4	34	4	115,3
5	2204	5	2285,3
6	17	6	98,3
7	1718	7	1799,3
8	3888	8	3969,3
9	1701	9	1782,3
10	0	10	81,3
11	0	11	81,3
12	0	12	81,3
-	-	13	81,3
-	-	14	0

8.5 Results of the Markov model

The final touch of the analysis is to give an incremental cost effectiveness ratio of the two strategies compared. As said before, in order to get the cost of the two strategies with a time horizon of 30 years, a trial version of the Data TreeAge Pro program has been used.

Rolling back the model for the no vaccination strategy a cost of 1,211.37 Euros is obtained. The cohort consists of 5,120 individuals aged 14 years in 2002, so the total cost of the no vaccination strategy is 6,202,215.09 euro. On the contrary the vaccination strategy will have a cost of 1,142.44 Euros, that multiplied by the amount of individuals (5120) will make a total cost of 5,849,311.79 Euros.

According to these results the vaccination strategy will turn out less costly than the no vaccination strategy taking into account a time horizon of 30 years where the individuals can suffer different health problems like the Herpes Zoster. The cost difference among the two alternatives is of 352,903.37 Euros. Navarre´s Health system will save 352,903.37 Euros in the long-run if the vaccination program is applied.

Additionally, the no vaccination strategy will result in that time horizon in 461 individuals infected, whereas in the vaccination strategy only 134 individuals will suffer Varicella. The vaccination strategy will then prevent 327 cases of Varicella.

These results can be interpreted using the cost-effectiveness plane explained in figure 1. The ICER diagram has four quadrants. The strategy of vaccination is less costly and more effective than the one of no vaccination; it means that the strategy will be situated in quadrant QII. All strategies situated in quadrant QII are dominant strategies since they increase effectiveness with lower costs. It can be said then that the vaccination strategy is dominant to the no vaccination strategy.

However, these results do not mean directly that the Health system will save that amount of money in practice. This happens because of the rigidity of the structure of the Health system. Where the resources saved might find it difficult to be assigned to alternative efficient uses. It is important to note that the economic evaluation assumes that savings will be assigned to alternative efficient uses.

Another consideration that might be of concern to the decision maker is the budget impact of the decision. To implement the vaccination strategy, there is a need of additional funds to finance the program. These might not be available. This suggests that economic evaluation should be accompanied by a budgetary impact analysis.

8.6 Limitations of the model

The availability of data for the costs and the Varicella and Herpes Zoster cases in Navarra was limited due to the lack of information. Additionally there is not a system to check the cases of Varicella, hospitalizations or Herpes Zoster by age group in Navarre.

The program used only allowed to introduce transactional probabilities that were equal for each Markov cycle. However, for instance the probability of suffering Herpes Zoster is not the same at all age ranges, so an average between all the conditional probabilities had to be made. The same happens for death, complicated Varicella and normal Varicella health states. This compromises the accuracy of the results.

The TreeAge program used to design and calculate the results of the Markov model was available only in a free limited version so most of the functions were limited.

9 CONCLUSIONS

Economic evaluations have been widely used to assess health decisions. Over the last few decades it has been given great importance to the study of the effectiveness of the Varicella vaccine. Most of those studies prove the effectiveness of the vaccine and situates it in a range of 70% to 90% of the cases.

Nowadays, researchers are focusing on the analysis of the cost-effectiveness of this vaccine. The Varicella virus, in the absence of vaccination, has a high incidence rate. In normal conditions the virus does not imply high costs. However, if complications appear health costs increase sharply. A patient with complicated Varicella stays an average of 7 days in hospital. Moreover, Varicella can reactivate in later life in the form of Herpes Zoster, which is a more serious disease with high hospitalization rates and costs for the health system. A patient with Herpes Zoster stays an average of 9 days in hospital; this fact increases health care costs.

The evidence shows that Varicella vaccine has helped to reduce the incidence of the chicken pox virus. Moreover, the hospitalization, complications and mortality rates have been reduced sharply. The vaccine is approximately effective in 91% of the cases. However, 24% of the vaccinated individuals present a weak Varicella called Varicella breakthrough. Nevertheless the Varicella breakthrough is milder than the normal Varicella so those cases are not considered as ineffective vaccines.

The critics of the Varicella vaccine were holding up to the argument that the vaccine contributed to the increase in Herpes Zoster incidence rates. However, the evidence also shows that there is no significant prove that Varicella vaccine contributes to the reactivation of the Varicella Zoster virus as Herpes Zoster in later life.

The purpose of this project was to study the Varicella virus and the Varicella vaccine. Additionally, the paper does a literature review about previous cost-effectiveness analysis of the vaccine in order to get a background and perform a similar analysis for the autonomous community of Navarre.

The cost effectiveness results measured in terms of incremental cost effectiveness ratios shows that Varicella vaccine can be cost- saving or not ,depending on the perspective taken and on the methodology used. Most of the studies mentioned in this project showed that from a health care´s perspective the Chicken pox vaccine shows a positive cost per case avoided for the health system. However, if the social perspective is taken, most of the studies conclude that the vaccine is cost saving.

The cost-effectiveness analysis performed in this final degree project for the case of Navarre concludes that the program will prevent 327 cases of Varicella. Additionally the Health system of Navarre will save, by applying the vaccination program, 352,903.37 Euros.

However, it is important to notice that the savings due to the vaccination program might find it difficult to be transferred in practice to other areas of the health system to be used efficiently. It will depend on the structure of the health system and the precedence of these costs. Nevertheless, these resources can be used for other health treatments. Even though, further analysis will be needed to see the real costs saving if taking into account the health system´s structure of Navarre.

The differences between the results in Spain and in the rest of the world, can be explained by the differences in the methodology used and in the perspectives taken. Most of the studies in the literature review use a decision tree analysis. On the contrary the cost-effectiveness analysis developed in this project uses a Markov model. Nevertheless, no matter the method used most of the studies of the varicella vaccine conclude, as ours, that the Varicella vaccine is cost-effective.

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11 ANNEXES

Annex 1. Probabilities and conditional probabilities of the Varicella complicated Varicella, death and Herpes Zoster for Spain.

Tabla 1. Cálculo de las probabilidades para cada rama del árbol de decisión mediante el teorema de Bayes

Grupos de edad (años)	Casos	Población	Tasa de incidencia	Porcentaje de población P (edad)	Incidencia acumulada P (varicela/edad$_i$)	Incidencia acumulada por porcentaje de población P (edad$_i$) × P (varicela/edad)	Probabilidad P (edad$_i$/varicela)
a) Varicela							
13-14	7.017	77.964	0,09	0,165	0,015	0,03	0,03
15-24	25.423	282.476	0,09	0,340	0,593	0,202	0,39
25-34	27.500	343.754	0,08	0,414	0,551	0,228	0,44
35-44	10.112	126.399	0,08	0,152	0,513	0,078	0,15
Total	70.052	830.593				0,523	
b) Complicaciones-hospitalización							
13-14	19	7.017	0,003	0,1002	0,0054	0,001	0,01
15-24	76	25.423	0,003	0,3629	0,0295	0,011	0,15
25-34	297	27.500	0,011	0,3926	0,1024	0,040	0,57
35-44	141	10.112	0,014	0,1443	0,1302	0,019	0,27
Total	533	70.052				0,070	
c) Mortalidad							
13-14	0	7.017	0,0000	0,100	0,0000	0,0000	0,00
15-24	1	25.423	0,0000	0,363	0,0004	0,0001	0,50
25-34	1	27.500	0,0000	0,393	0,0004	0,0001	0,50
35-44	0	10.112	0,0000	0,144	0,0000	0,0000	0,00
Total	2	70.052				0,0003	
d) Herpes zoster							
13-14	1.104	788.301	0,0014	0,042	0,0028	0,000	0,01
15-24	7.435	5.310.546	0,0014	0,282	0,0139	0,004	0,22
25-34	13.716	6.531.321	0,0021	0,347	0,0208	0,007	0,40
35-44	13.006	6.193.567	0,0021	0,329	0,0208	0,007	0,38
Total	35.261	18.823.735				0,018	

$$P\,(edad_i/varicela) = \frac{P\,(edad_i) \times P\,(varicela/edad_i)}{\Sigma\, P(edad_i) \times P\,(varicela/edad_i)}$$

Source: Peña Rey, I., Pérez Farinós, N., Cortés García, M., & Amela Heras, C. (2004). Coste- efectividad de la vacunación contra la varicela en adolescentes en España. *Gaceta Sanitaria* , v.18 n.4.