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Price-Effectiveness: Pharmacoeconomics, value and the right price for HPV vaccines

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Abstract

Drawing on a pragmatist approach to pricing this article discusses the impact of cost-effectiveness analysis in the pricing strategies of pharmaceutical companies. Through an analysis of the human papillomavirus vaccination, this article illustrates the strategic appropriation of evidence based medicine (narratives and practices) that pharmaceutical companies have undertaken to enhance the value of their products. While governments are concentrated on the measurement of costs and efficiency (cost-effectiveness), companies attempt to find the threshold of effectiveness that supports their estimation of value. I have called such mode of calculation, price-effectiveness. Pharmaceutical companies engage in different ways with cost-effectiveness analysis in devising their own price strategies. First, cost-effectiveness analysis is used as an instrument to raise HPV vaccines as a matter of interest for health authorities. Second, companies produce models to maximise the effectiveness of their products. Third, the expense side of cost-effectiveness analysis has opened an opportunity to represent some conditions as diseases in order to increase the potential value of the vaccine, expressed in a higher price. Debates and practices of pricing offer a unique opportunity to trace how particular forms of quantification have become the common ground in the demonstration of value in healthcare and the adaptation of companies.

Keywords: pricing, value, vaccines, valuation, human papillomavirus vaccine

1 Introduction

The price of vaccines is a contested issue. While pharmaceutical companies complain about price control, researchers and health officials have criticised the lack of transparency in the pricing of vaccines and the lack of information about the agreements reached with governments and pharmaceutical companies' margins of profit (Godlee 2011; Hecht and Schmidt 2011; Garattini et al. 2012). The pricing of drugs, and in particular vaccines, is a black box.

In such situations, the different actors involved in the economical exchange produce strategies to guess and to estimate the valuation of each other to reach the correct price of negotiation. Governments and companies have used calculation techniques from operations research (Robbins and Jacobson 2015) and health economics (Gregson et al. 2005) to demonstrate the validity of their own estimations of value, and to capture others valuations. From the perspective of national governments this has involved the use of cost-effectiveness analysis and the use of health adjusted metrics such as quality adjusted life years (QALY) and disability adjusted life years (DALY). From the perspective of the manufacturer, these tools have sometimes been called pharmacoeconomics (Gregson et al. 2005). This kind of analytics examines the pricing from a manufacturer´s perspective, investigating the maximum inclusion price, that is, the highest price at which the vaccine is still selected by a customer (Robbins and Jacobson, 2015). Pharmacoeconomics' practitioners argue they practise reverse engineering to determine the factors that influence aligning a particular vaccine to a particular price (Robbins and Jacobson 2015; Gregson et al. 2005). In other cases, pharmaceutical companies actively sponsor or develop in house their own cost-effectiveness analysis (CEA) in order to highlight the effectiveness of their products and the savings that can be generated for healthcare insurers and governments despite high introductory prices.

As valuation studies have pointed out, the relations between price and value are very important in understanding the ways in which economic valuation interacts with other ways of enacting value (Kjellberg and Mallard 2013; Roscoe 2013; Dussauge et al. 2015). Different authors (Harrison and Mort 1998; Mol 2008; Moreira 2012; Nord, 2005; Geiger et al., 2014) have presented the practical limitations of using conventional monetary prices to estimate the value of health, the quality of life and the costs of disease and death. Health currencies such as QALY and DALY are attempts to produce metrics of value different from that of money. However, such disentanglement of monetary units from other metrics is partial and momentary. Prices are constantly entangled in these calculations and constitute the privileged way of communicating to the 'public' the value of health interventions.

This paper discusses the ways in which pharmaceutical companies have enacted relations between price and value in the case of Gardasil[1] (a tetravalent HPV vaccine manufactured by Merck), presenting the uses of CEA and the medical evidence repertoire in the calculation of prices. In particular this article describes the role of CEA in the enactment of the value of vaccination and the ways in which such valuations are integrated into a wider strategy of pricing for pharmaceutical companies. Debates and practices of pricing offer a unique opportunity to trace the role of quantification and calculation in the demonstrations of value that different agents undertake.

Pharmaceutical companies are not very transparent in relation to the practices that they use to define the price of their products. Pricing transparency has been a matter of debate in different countries (Godlee 2011; Hecht and Schmidt 2011; Garattini et al. 2012). The analysis of pricing and pharmacoeconomics that I present in this article has been conducted by reconstituting pricing strategies through academic literature, particularly articles about cost-effectiveness and pricing of HPV vaccines published in the journal *Value in Health*, official publication of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). This analysis attempts to address the valuation frameworks developed in nationally located negotiations about price and pertinence of the HPV vaccination.

In what follows, I briefly present some of the concepts in understanding pricing as a valuation practice (Tryggestad 2005; Çalişkan and Callon 2009, 2010; Roscoe 2013; Dussauge et al. 2015). Drawing on Çalişkan and Callon's (2010) invitation to analyse pricing, I present some of the tensions that remain in the health economics account for HPV vaccine prices. I argue that while the public sector's use of health economics is focused on the measurement of costs and efficiency (cost-effectiveness), companies attempt to find the threshold of effectiveness and cost that supports the highest price. I have called such mode of calculation, price-effectiveness.

2 Pricing as valuation practice

Prices and price settings are important elements in the organisation of healthcare as a market (Sjögren and Helgesson 2007; Moreira 2012; Roscoe 2013). Çalişkan and Callon (2009) have noted that 'the existence of a market implies that the valuations, and the calculations that produce them, come out in the form of prices' (2009, 17). They have suggested the term valorimeters to denote 'tools, procedures, machines, instruments or, more generally, devices effecting this controversial translation of values into figures and, more precisely, into monetary amounts' (2010, 17). Devices such as DALYs, CEA and micro-costing can be understood as valorimeters. They entangle different objects in order to enact evidence, effectiveness and statistical representativeness and they present such enactments as numbers, figures and monetary amounts.

[1] Gardasil protects against four types (tetravalent) of HPV: HPV 6 and 11 associated with genital warts and HPV 16 and 18 associated with cervical cancer. Cervarix protects against two types (bivalent) of HPV: HPV 16 and 18.

Economic anthropology (Zelizer 1998; Hénaff 2010) has shown the ways in which price and price setting are attached to moral dynamics and mediate political and symbolic relations deeply entangled within *economic* exchanges. For instance, the problem of price opens up discussion about the distinction between (public or common) good and goods. That is the differentiation between things that are individually consumed (goods) and things that enact for society´s benefit (good), and between commodities (things with prices) and gifts (altruistic objects) (Waldby and Mitchell 2006). The value expressed in these entanglements is much more complex than that considered by neoclassical economics when it understands the relation of price–value as willingness to pay and equilibrium between demand and supply.

Pricing in healthcare is a complex task; it involves the development of models that tame relationships and objects in order to entangle them as economic facts. As Roscoe notes, economic facts created by modelling 'travel, unquestioned, into subsequent models and debate despite being often unstable and contested' (Roscoe 2013, 388). Through practices such as pricing, economics deduces 'ought' from 'might be'. Moral questions become empirical matters (2013, 389).

Pricing models render visible the relationships that constitute markets (Dussauge et al. 2015). Pricing strategies are diverse; some of them model supply and demand in order to reach a hypothetical price. From contingent and arbitrary assumptions, models configure 'objective' facts.

> In each case we can witness the career of the fact: the modelling which results in a price; the severance of that price from the often questionable and arbitrary circumstances of its birth; and the utilisation of the fact as it travels into other models, discussions, and arguments. (Roscoe 2013, 390)

Different authors have noted that prices, as results of models and numerical artefacts, provide an account of the ways in which economics colonise social relations and perform economic objects (Roth 2002; Tryggestad 2005; Roscoe 2013). As Tryggestad has noted in relation to natural prices, calculation constitutes an act of purification. While actual or market prices are defined by a particular relation between the price and the good sold on the market by a producer, natural prices do not denote this kind of particular identity relation, but a general one (Tryggestad 2005, 594).

Roscoe has addressed the role of pricing in the constitution of markets, particularly by engaging in discussions about prices in organ donation. He describes how in order to establish supply, economists use tools such as the contingent valuation method (CVM), in which people are asked about their willingness to pay (WTP) to obtain goods and willingness to accept (WTA) to give up the goods. A supply curve is statistically produced to represent such answers (Roscoe 2013, 390). Such prices are disentangled 'from their roots in social settings and moral contexts' (2013, 388). However once this happens, prices 'immediately assume moral force' (2013, 388).

These works have shown the ways in which price performs value showing the rhetorical force and linguistic power of economics. 'Economic values are parsimoniously expressed as numbers: expressions of preference contained in price' (Roscoe 2013, 397). Prices affect the practices and considerations of the agents that are engaged in producing them. Prices can be addressed as quantified qualifications of different values; however, such character is performed in practice, in the particular and local settings in which valuations happen (Muniesa 2007).

HPV vaccines are goods whose inclusion in public healthcare programmes has involved their enactment as a public good. Calculation devices such as CEA make such *transformation* possible. The calculation and negotiation of prices of HPV vaccines is one of the strategies to

make them a matter of concern. Pricing in the context of public policy and state interventions renders visible the boundaries and the problems that a radical distinction between market and public sector entails. From the perspective of pharmaceutical companies, the public sector is characterised as a market, and CEA is one of the different strategies of production of value developed to negotiate with governments about the right price of vaccination.

HPV vaccines pricing is a process of engineering (Roth 2002; Roscoe 2013). The pricing of this healthcare technology has involved the use of the calculative infrastructure of healthcare economics, relying on algorithms such as the Markov chain models rather than abstractions of supply and demand (Roscoe 2013, 394). Such calculation strategies show the ways in which *evidence-based medicine* (EBM) is shaping practices and languages to legitimate particular estimations of value that are confronted in markets. Pharmaceutical companies have appropriated devices of calculation used by public agencies to enhance their own valuations.

Although prices expressed as monetary measurements do not seem to be the right language in which to talk about human life and its quality, they are the most direct and clear way of communicating the 'value' of a particular entity. Metrics based on the quantification of quality of life such as DALY and QALY are translated at some point into monetary amounts. In public arenas prices, costs, investments and savings of money are the privileged enactments for communicating the value of HPV vaccines and the arguments of the State. By analysing the 'value based approach' and the use of CEA by pharmaceutical companies I explore the ways in which prices and monetary estimations are entangled with other metrics and narratives in order to perform the value of HPV vaccines as healthcare entities.

A closer examination of these practices contributes to understanding the role of quantification and quantified entities in the shaping of contemporary healthcare governance (Porter 1995; Moreira 2012). In what follows, I describe some of the problems that the pricing of HPV vaccines open up in relation to the valuation and shaping of healthcare markets. As Sjögren and Helgesson have noted, in markets pricing is a central activity in which the qualities of goods are settled, and who should pay which price for what is decided (Sjögren and Helgesson 2007, 215).

3 HPV vaccines, cost-effectiveness analysis and pricing

HPV vaccines offer an interesting case to follow these valuations in practice. These vaccines have been adverted mainly as a prevention tool against cervical cancer, which is strongly associated with the persistent and untreated infection with specific types of HPV (most frequently types 16 and 18). There are currently two vaccines in the market that protect against both HPV 16 and 18, which are associated with 70% of cervical cancers worldwide (WHO 2013): Gardasil® produced by Merck; and Cervarix®, produced by Glaxo SmithKline.

HPV vaccines are the most expensive vaccines on the market (Garattini et al. 2012; PAHO 2013; CDC 2014). In the US Gardasil® costs for instance, US$121 per dose for the CDC and US$141.38 for the private sector (Robbins and Jacobson 2015). Despite the reduction in price for developing countries (PAHO 2013; GAVI 2014), HPV vaccines remain a very expensive intervention if the price of other vaccines and the size of the vaccination programmes – that entail the use of millions of doses per year – are considered. The impact of the introduction of these technologies in governments' budgets have demanded the development of 'justifications', strategies of valuation that render visible the contribution of this expense (investment) to the public good.

The price of vaccines varies among countries because each one is treated as a particular and different market. At the same time these differences are understood as local expressions of global price interdependency. Companies keep a global perspective to define market segments and to make decisions about the *right* price. The evolution of the prices of HPV vaccines

shows the ways in which prices are organised following a political pattern; the distinction between countries and markets according to classifications based on income of each country is clear. The price of HPV vaccines is higher in high-income countries such as the United States, Canada and European countries; middle income countries such as South Africa, Mexico, Argentina and Colombia have to pay prices between US$35 and US$14. Finally, HPV vaccines in poor countries are priced with the mediation of the GAVI Alliance and are in the range of US$ 5–10.

The high cost of introducing and maintaining a highly effective strategy of prevention of cervical cancer – screening programmes – has demanded the use of CEA. CEA allows decisions to be made about the benefits of the vaccination in terms of reduction of the burden of cervical cancer (Maldonado 2015). It has shaped discussions about the value of HPV vaccines, promising the efficient use of limited resources based on the best evidence. Evidence-based medicine experts and policymakers argue that CEA is the tool to reveal if the cost of a new therapy is 'worth it' or if decision makers should be paying for some other, 'cheaper' or 'more effective therapy'. Pharmaceutical companies have responded to this framework by expressing their own estimations of value in the same language: cost-effectiveness, burden of disease and social value.

CEA allows the identification and monetization of the costs and the benefits of intervention. It relates costs to specific measures of effectiveness, in the case of health economics to measures of human life´s value expressed in QALY, DALY or years of lost life (YLL). Such metrics have promised 'to revolutionize the ways in which we measure the impact of disease, how we choose interventions, and how we track the success or failure of our intervention' (Foege 1994, 1705 quoted in Anand and Hanson 1997, 686). CEA is a powerful tool in policymaking because it translates different objects and realms into a quantified language whose 'value' is perceived as highly visible: money. CEA is a device of commensurability. As Ashmore and colleagues note, the success and credibility of CEA 'lies in their ability to continually trade between the worlds of facts and figures and worlds of words and politics' (Ashmore et al. 1989, 24).

Health economics literature claims that the pricing of vaccines is a complicated process with scientific, medical and public health ramifications. Different authors (Gregson et al. 2005; Lee and McGlone 2010; Garattini et al. 2012; Robbins and Jacobson 2015) have warned about the considerable impact of pricing on new vaccine adoption. In that regard, considerations about health and medicine as a public good and the interest of the industry in producing profits have often clashed. The rise of EBM has been linked to the promise of providing calculative tools to defend public interest from the profit interest of companies (Garattini et al. 2012). In response, pharmaceutical companies have assimilated the language and practices of calculation of EBM as a new way of interacting with governments and healthcare authorities. This mode of valuation has made extensive use of analytical tools from operations research (Weniger et al. 1998; Jacobson 2012; Postma et al. 2013; Newall et al. 2014; Robbins and Jacobson 2015) and health economics (Jacobson and Sewell 2002; Ehreth 2003; Gregson et al. 2005; Chuck et al. 2010; Danzon et al., 2011). Pharmacoeconomics can be understood as a response by the pharmaceutical industry to changes in healthcare decision making; in particular regarding the introduction of cost-effectiveness and price control. Gregson and colleagues (2005) call such approach: value-based pricing. For them, the pricing of health technologies is moving from cost-based pricing to value-based approaches. While a cost-based approach defines price as equal to cost (C) plus profit (I):

$$P=C+I$$

From a phamacoeconomics approach that claims to be the market´s perspective, value (V) is equal to reference price (R) plus/minus differential value (D):

V=R+/-D

In this logic price should reflect (social) value. As is noted by Gregson and colleagues (2005), 'the appeal of this simple framework is that it intuitively fits with how we, as consumers and "purchase decision-makers", evaluate price as part of purchase decisions, whether consciously or subconsciously' (Gregson et al. 2005, 122). They argue that the fundamental pricing question has shifted from 'What price do we need to charge to cover our costs and make a good return?' to 'Given market perceptions of value, which products can we profitably produce?'(2005, 122).

Other authors such as Lee and McGlone (2010) have described the pricing of vaccines in terms of a linear process that comprises the following components: target population analysis; identification of potential competitors and alternatives; vaccine target product profile (TPP) and comparing it to projected or actual TPPs of competing vaccines; quantifying the incremental value of characteristics of new vaccines; determining vaccine positioning in the marketplace; estimating the vaccine price–demand curve; calculating vaccine costs; accounting for various legal, regulatory, third party payer and competitor factors; considering the overall product portfolio; setting pricing objectives and selecting pricing and pricing structure (Lee and McGlone 2010: 619).

Gardasil in particular has attracted the attention of the pricing literature in vaccine economics. Lee and McGlone refer to three major 'pricing revolutions' – considerable jumps in new vaccine pricing in the vaccine industry over the past three decades: in the 1980s hepatitis B virus vaccine (Merck) at US$100 per series; in 2000 pneumococcal vaccine Prevnar® (Wyeth) at US$250 per series; and in 2006 Merck's HPV vaccine Gardasil® at US$450/series. Lee and McGlone note that in all three cases, 'pricing the new vaccine at a much higher price than other existing vaccines seemed risky but eventually led to increased investment in the vaccine industry and transformed these vaccines into "blockbusters" with sales over $1 billion' (Lee and McGlone, 2010, 621).

The characteristics of Gardasil but particularly the temporality of cervical cancer has demanded a complex modelling of the impact of vaccines to support such a high price (Merck 10-K, 2007). In the US for instance, reimbursement was a key issue. Insurance companies had not reimbursed such an expensive vaccine before, and because of the long and uncertain period between HPV infection and the development of cancer (20–30 years), the reduction of healthcare expenditures would not be expected in the near future (Canfell et al. 2012). The pricing strategy relied on capture and anticipated health impacts, and economic saving.

Part of the strategy has involved accounting for various legal, regulatory and third-party payer considerations. Prior to Gardasil's FDA approval for 9–26-year-old females in 2006, Merck designed an extensive strategy to lobby state legislatures throughout the US to rule HPV vaccination for school entry, requiring insurance companies to cover HPV vaccine, or allocate state funds for vaccination or to promote awareness of the vaccine (Lee and McGlone 2010, 622). Although such aggressive lobbying generated some resistance among some physicians and public health officials, it promoted many legislative initiatives to support the relatively high price of Gardasil (2010, 622).

Such a strategy was also used in developing countries; in Latin America for instance, parallel to the economic analysis of HPV vaccines' cost-effectiveness, politicians promoted bills to support public HPV vaccination programmes regardless of economists' arguments. Often such enthusiasm created clashes between experts and politicians (Maldonado 2015).

The other element is the economic valuation of the HPV vaccination in terms of the burden of disease reduction and the estimation of the monetary saving of such impact. So-called value-based pricing links monetary expressions of value-as-price to the social and material benefits

claimed by drug and health interventions. As is noted previously, such pricing calculations are shaped by EBM language and techniques. The political and economic elements of pricing strategies are deeply entangled. The economic and epidemiological justification of HPV vaccines is a key element in political and public discussions about the pertinence of public sponsored vaccination.

In what follows I present three ways of tracing such entanglements and particularly to show the role of CEA in the strategic pricing of HPV vaccines. First, CEA is used as an instrument to produce matters of fact about the impact of vaccines, and to raise vaccines as matters of concern for health authorities. Second, companies produce models to maximise the effectiveness of their products; vaccine price can potentially rise insofar as its effectiveness increases. Pharmaceutical companies not only organise and design the clinical trials that produce input data for modelling, they also create statistical arrangements that make visible and sometimes boost vaccine performance data. Third, the cost side of the CEA equation has opened up an opportunity to represent particular conditions as diseases in order to increase the potential value of the vaccine. In the case of Gardasil, the introduction of genital warts as a health concern has been achieved through the accounting of its costs. The protection that Gardasil provides against genital warts has been a key differential element against its competitor, Cervarix. At the same time, Gardasil's interest in genital warts has coincided with genital warts' transformation from a benign condition to a public health problem.

4 Cost-effectiveness analysis and the constitution of HPV vaccines as matter of concern

Vaccines have been one of the most preferred subjects of concern to CEA. Because most vaccines are prophylactics, drugs to create immunity, they are an excellent case for demonstrating the (economic) benefits of prevention and the utility of CEA as decision-making tool. Since the 1990s the literature about the CEA of vaccines has grown; however, such trends reached a peak around the middle of the 2000s with the introduction of HPV vaccines onto the market and in public discussions about their affordability, safety and efficiency. As soon as Gardasil® was approved by the US Food and Drug Administration (FDA) in 2005, different voices were raised in favour of its introduction in different countries both in the North (Canfell et al. 2012) and in the South (de la Hoz et al. 2016). Figure 1 shows the increase in articles both about vaccines and HPV vaccines' cost-effectiveness. A further source for observing the increasing attention on CEA in negotiations about vaccines' affordability is the journal *Values in Health*.

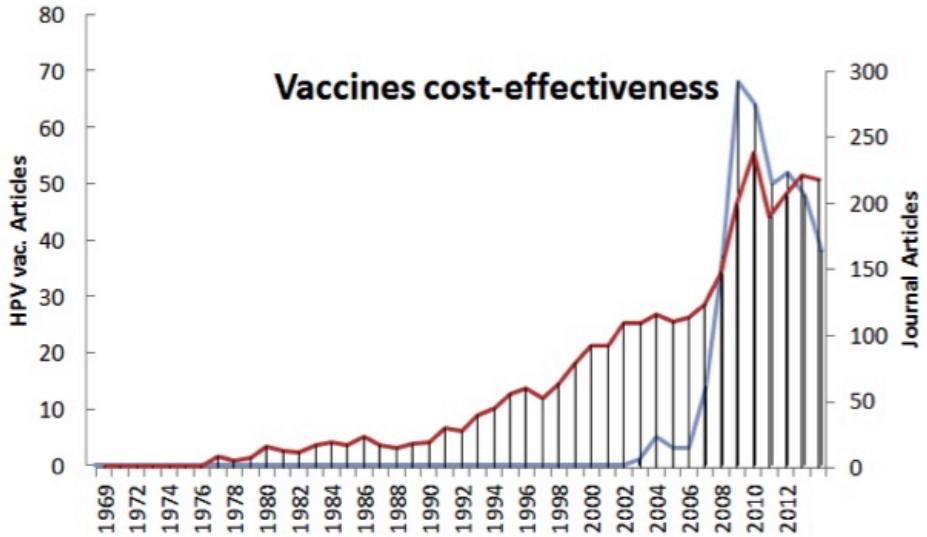

Figure 1. Journal articles about vaccines' cost-effectiveness
Note: Journal articles about vaccines' cost-effectiveness (red-right axis) and about HPV vaccine cost-effectiveness (blue-left axis).
Source: Author's calculations based on information retrieved from Pubmed database in 2014.

Values in Health is the journal of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) covering the areas of pharmacoeconomics (health economics) and outcomes research (clinical, economic and patient-reported outcomes research). In contrast with the Pubmed figure in which the literature about HPV vaccine CEA is still growing, *Value in Health* shows a normal distribution that peaked in 2010. Such a peak coincides with a critical time in the introduction of HPV vaccines in publicly funded programmes in developed countries and with the first discussions about their introduction in middle-income countries.

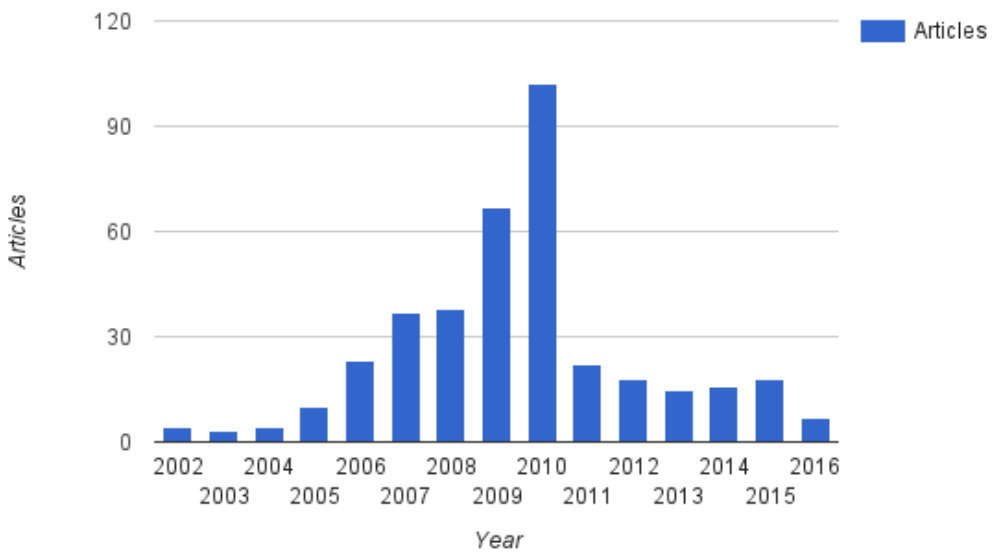

Figure 2. Journal articles about HPV vaccines' cost-effectiveness in *Value in Health*
Source: Author's calculations based on information retrieved from ISPOR database in 2016.

A more detailed approach to this literature shows how CEA precedes technical and political debates and discussions about HPV vaccines, raising their profile and informing practitioners and decision makers about the advantages of this technology. For instance, in the case of *Value in Health* the first articles about the cost-effectiveness of tetravalent HPV vaccine (Gardasil) were published in 2002. Most of them, in an abstract way, present the potential savings of a vaccine in process of approval that has the potential of attacking cervical cancer, reducing not only its mortality but also the consequences of false positives. Other studies have addressed the impact of extending the vaccination to women over the age of 26, and to men (12–18 years old) and more recently the cost-effectiveness of Gardasil 9, a nonavalent HPV vaccine (HPV 6, 11, 16, 18, 31, 33, 45, 52 and 58), that promises to tackle 90% of HPV viruses linked to cancer worldwide. Some of these studies are developed in-house by pharmaceutical companies or through consultant firms; however, most of the studies are developed by universities and research centres in which at least one of the authors declares links with Merck or GSK. In all these cases, CEA has meant the reinterpretation of prevention, its risks and anxieties, through the language and the logics of economic valuation.

Considerations about hypothetical prices precede CEA; however, one of the effects of determining cost-effectiveness is stating the willingness to pay of governments and therefore a limit of negotiation about the public price of vaccination. During the last five years, HPV vaccination of girls has been introduced in most developed countries, supported by models that have almost universally found vaccination of pre-adolescent females to be cost-effective (Canfell et al. 2012). In developed countries the assumed cost per vaccinated individual (CVI per 3 doses of the vaccine and other costs such as vaccine wastage, freight, supplies and administration) varied from US$360–500 in evaluations for North America conducted from 2008; from €232–480 in Europe; and from £235–282 in the UK. CVI, the estimated price of the vaccine, is an important determinant of the cost-effectiveness of vaccination. For instance, one study in Canada estimated that the cost per QALY gained by Gardasil vaccination of 12-year-old girls was CAN$20,500 when the CVI was CAN$400, and that 'each decrease of CAN$50 in the CVI would reduce the cost per QALY gained by about CAN$3000'(Brisson et al. 2007).

In parallel to the discussions held by developed countries, the World Health Organization (WHO) and the Pan American Health Organization (PAHO) began to develop guidelines and conferences to prepare middle-income countries in the adoption of the vaccines (WHO 2007). These different voices pointed out the massive benefits of vaccination in the reduction and eventual eradication of cervical cancer, but at the same time warned about its high costs and the need for careful decision making. In 2008 the PAHO asked the Sabin Institute in the US to study the burden of the disease of cervical cancer and HPV infection in six countries of Latin America (Argentina, Brazil, Chile, Colombia, Mexico and Peru) and conduct a CEA of the HPV vaccines at different price scenarios. The study concludes that only vaccination programmes below US$20 per doses are cost-effective for these countries.

In Latin America, for instance, most CEAs are based on the PAHO study. The study gathers data about the costs of surgeries, cervical screening programmes and medicines in Argentina, Brazil, Chile, Colombia, Mexico and Peru. This study constitutes the only source to estimate the cost of treatments in the region. It translates the different costs linked to cervical cancer detection and treatment into international dollars (I$), an analytic currency recommended by WHO to establish international comparison between healthcare procedures. 'The majority of this treatment cost was attributed to the costs of hospital stay and palliative care' (PAHO and Sabin 2008, 9).

Although CEA models are very sensitive to changes in the estimated price, the incremental cost-effectiveness ratio (ICER), the number that expresses the cost-effectiveness of a health technology, varies depending on a range of factors that influences the estimated impact of the vaccine and that can sustain its cost-effectiveness, despite high prices. As is presented in Section 5, numbers in relation to vaccine efficacy, duration of protection, health outcomes included in the analysis, and burden of disease in the absence of vaccination have a key role in potentially increasing the estimation of effectiveness. Section 5 illustrates the tensions between public agencies and manufacturers in the effort to calibrate models that reflect their own estimations of value.

5 The devil is in the detail, economic engineering and contested effectiveness

Pricing equations simplifies the complex assemblage configured by modelling. The starting point of the calculation strategy depicted by Gregson and colleagues is to define reference price. They argue that the reference product is generally the present standard of care. In practice the modelling of the impact of the HPV vaccine offers a different solution to cervical cancer treatment, moving the healthcare strategy from cure to prevention. In relation to cervical cancer the standard of care encompasses a heterogeneous set of treatments and technologies such as national cervical screening programmes (CSP), radiation, surgery and chemotherapy depending on the stage of the disease. HPV vaccines promise a simplified new standard of care based on the immunisation and control of HPV infection.

Cervical cancer, within the pricing strategy, is understood in terms of the impact that the disease has on a population's dynamic described in morbidity, mortality and the burden of disease. These are key elements in the definition of a reference price. In the case of Gardasil®, Merck calculated the price based on the money the vaccine could save for the entire healthcare system. The price should reflect the value of the vaccine, understood in this case as the contribution in terms of disability and death avoided, as well as the economics of saving for those who pay. These are the same calculations that are done by technical committees and government agencies in order to define the cost-effectiveness of such healthcare intervention. The other factor is the differential value. Such value is estimated through a mixture of data that justify clinical, economic and quality-of-life *improvements*. The objective of such calculations is to demonstrate the additional value that the new technology entails.

Such value is demonstrated through mathematical modelling. Pharmaceutical companies provide the input data of those models through randomized clinical trials (RCT) developed to obtain licences for their products. These studies produce numbers about safety and effectiveness. Such data are combined in models with epidemiological statistics about the population target, incidence and prevalence of infection, mortality and morbidity by cervical cancer among others.

Most of CEA of HPV vaccines are produced through Markov chain cohort models. A cohort model simulates a single birth cohort of people through their lives. 'In cohort models of HPV-related disease, the probability of incident infection is usually modeled as being dependent on age, but age-specific infection does not change over time' (Canfell et al. 2012, 15). Some authors argue that these models underestimate the overall effects of HPV vaccination because they cannot capture the changing effect of vaccination over time. Particularly they are not able to capture the herd immunity produced by the immunisation. In spite of these limitations, most of CEA have found the vaccination of pre-adolescent girls highly cost-effective, particularly by the saving on the treatment of precancerous lesions, genital warts (in the case of Gardasil) and false positives.

Woertan and van der Wilt (2013) argue that the frequentist interpretation of probability in the design of CEA tends to favour the estimation of value of pharmaceutical companies, statistically increasing the effectiveness of vaccination and therefore supporting higher prices for HPV vaccines. They offer an interesting account of the ways in which pharmaceutical companies present statistics to support their estimation of value, using the language of decision makers and the complexities of negotiating the prices of vaccines. The devil is in the detail.

In 2007 and 2008, CVZ (now Zorginstituut Nederland) issued two advices to the Dutch Minister of Health about the reimbursement of Gardasil. In 2007, CVZ recommended that Gardasil should not be reimbursed. CVZ acknowledged the medical value of Gardasil, but not its cost-effectiveness. Nevertheless, that year the 'Dutch Health Council recommended including HPV vaccination in the national vaccination program for 12-year-old girls and that girls who were then 13 to 16 years old would also be eligible for vaccination' (Woertan and van der Wilt 2013, 605).

In 2008, Merck asked for a reassessment of Gardasil, arguing that the vaccine should be reimbursed for 17–18-year-old girls as well. Once more, CVZ advised not to reimburse Gardasil. CVZ questioned the effectiveness of the vaccine that was used in the cost-effectiveness model provided by Merck. First, the manufacturer's model used the per-protocol susceptible effectiveness from one of its clinical trials (FUTURE I and II); CVZ considered such assumption to be overly optimistic. Second, in the new model developed by Merck, HPV 16–18 prevalence was corrected; however, CVZ maintained that such an assumption was not sufficiently supported by data. 'In both advices, the evidence came from a variety of sources, and was analyzed with standard frequentist methods' (Woertan and van der Wilt 2013, 605).

Woertan and van der Wilt use a Bayesian approach to reanalyse the data underlying the CVZ decision about Gardasil. They argue that in these models none of the population used in the trials is representative of the actual target population that the vaccination programme will be applied to. They restructure the data reweighing the sub-populations by using HPV prevalence data to estimate the effectiveness that can be expected in the actual target population. While the original data show an effectiveness of 44% in the entire population and an effectiveness of 98% for women HPV-free at the start of the study, they found a mean effectiveness of 25%, and the probability that the effectiveness in the target population exceeds 50% is virtually zero. 'Conceivably, having the outcomes from our supplementary

analysis would have changed CVZ's opinion about the prophylactic effectiveness of Gardasil' (Woertan and van der Wilt 2013, 609).

Woertan and van der Wilt's analysis illustrates how the price and the production of value are negotiated in the details of modelling; CEA is a ground of negotiation in which numbers and probability are arranged in a way in which the valuation by manufacturers is enhanced. The last part of this article expands on the production of matters of concern by numbers, its role in the valuation of HPV vaccines and the ways in which such calculations are attached to prices. The rise of genital warts as a public health concern illustrates the strategic use of CEA by manufacturers to justify the value of their products and the consequences of this valuation in the transformation of biological conditions into medically recognized diseases. HPV vaccines were produced around cervical cancer prevention.

6 Generative modelling: Creating public health concerns by numbers

Although in principle the interest of healthcare authorities and governments in these vaccines was based on their promise of prevention against cervical cancer, genital warts became a decisive factor in the selection of Gardasil as a vaccine for national vaccination programmes. For instance, in 2012 the UK Department of Health changed from Cervarix® to Gardasil®, after a discussion about the burden of genital warts and its cost of treatment (Department of Health, Reference: 16896). The same has occurred in Latin American countries such as Colombia in which genital warts were a key element in the choice and justification of Gardasil® as a public health tool.

The enhancement of the cost-effectiveness of Gardasil by the inclusion of the prevention of genital warts is part of its pricing strategy. Studies about the burden of disease and the economic impact of genital warts are scarce, particularly before the development of this vaccine. For instance, a German study (Hillemanns et al. 2008), extensively used to estimate the possible impact of genital warts, was developed by MAPI Values (Health economics consultancy company) and funded and reviewed by Sanofi Pasteur MSD, the manufacturer of Gardasil® in Europe. A case that illustrates how numbers in CEA have an important role in the production of public health concerns and in the enhancement of drugs value is the estimation of genital warts in the introduction of Gardasil into the Colombian programme of immunisations.

In 2009 INVIMA – the Colombian food and drugs authority– approved Gardasil. After that, private clinics and medical insurance companies began to promote the vaccination for their female patients. The price of the vaccine, approximately US$150 per dose, limited access to the urban middle classes. Since 2010, different local authorities have started discussions about the importance of organising public, free vaccination programmes. The Expanded Programme of Immunisation entered into an agreement with the Universidad Nacional de Colombia to develop a technical study about the cost-effectiveness of HPV vaccines. This study considered the effectiveness of a national screening programme and of the international cost of vaccines on the market (Gardasil and Cervarix), concluding that at the international prices at that time (2009), a national HPV vaccination programme was not cost-effective (UNAL 2009, 60). Many voices within the medical community expressed disappointment with the conclusions of that study. However, the ruling of the Council of State to a class action was the event that forced reconsideration of the study results by the government. In 2011, the Ministry of Health asked the Universidad Nacional for a second technical study. This second study included an analysis of the burden of genital warts and concluded that at the international prices at that time (2011), an HPV vaccination programme using Gardasil was cost-effective.

The first study (UNAL 2009) was focused on defining the burden of cervical cancer and HPV infection, and the potential impact of HPV vaccines in reducing cervical cancer. This study was very careful in declaring the limitations and contingencies of the analysis. It notes the lack of official data about the national incidence and prevalence of cervical cancer and HPV

infection by types. It is stated, moreover, that the frequency of HPV 16 and 18 oscillates between 52% and 64% in the Colombian female population. More importantly, the study does not 'take into consideration the burden of disease produced by genital warts because these lesions are benign and there is no consensus about the degree of disability they produce' (UNAL 2009, 44).

After the ruling of the Council of State, genital warts surged as a matter of concern in relation to public health and as a decisive element in the choice of the right vaccine. In the second study, genital warts are the key element of differentiation and added value for Gardasil. Such context demanded metrics sensitive to subtle differences that are not perceived by measurement units such as LLY. DALY as a measurement unit of disability was considered the right tool with which to assess the burden of a disease of which the outcomes were not fatal. DALY allowed a more visible differentiation between vaccines to be produced. In terms of deaths avoided by vaccination, the performance of both vaccines was impressively similar. If Gardasil is compared with no intervention, in a cohort of 450,000 women this vaccine avoids 8783 deaths from the 9593 deaths that could happen without any intervention. In the same scenario, Cervarix avoids 8785 deaths. In contrast, when DALYS are introduced the gap between vaccines is rendered visible. Gardasil prevents 1054 DALYS as opposed to Cervarix's 1013 DALYS. Even though this difference is not very wide (41 avoided DALY) it is still bigger than the gap in terms of the reduction in mortality.

The nature of genital warts as a disease with a significant burden has been contested. There is no defined weighting for this condition within the technical literature about the burden of disease (VSG 2001, 1994; WHO 2012). Even the first of the Universidad Nacional's studies pointed out that such a condition is considered a 'benign' affliction. In the second study data are not provided about the assigned weight of genital warts in the calculation of DALY. Nevertheless, if the calculations are re-enacted it is possible to note that the disability value assigned is very low: just 41 DALYS are assigned to 8410 episodes of genital warts. Because genital warts are not a fatal condition, it is possible to estimate that the assigned disability weight was 0.0048. This weight is slightly higher than the lowest weighting assigned to a disease by the Victorian Burden of Disease (VSG 2001), which is the long-term effect of moderate burns. The interest in genital warts is a consequence of the introduction of HPV vaccines. The estimation of genital warts as a burdensome disease in CEA is part of the strategy of Merck to add value to its vaccine.

7 Discussion

As Çalişkan and Callon have noted,

> the actors themselves directly link the question of the fairness of prices to the content and construction of formulas serving to calculate them: it is not the prices that are fair or unfair, but their modalities of calculation, i.e. their formulas. (Çalişkan and Callon 2010, 18)

CEA is the modality of calculation that has configured the negotiation and discussions about HPV vaccine's price. The repertoires of EBM have shaped the strategies of pricing of pharmaceutical companies. EBM has provided practices and language to legitimate particular estimations of value that are confronted in markets. Pharmaceutical companies have appropriated devices of calculation used by public agencies to enhance their own valuations and to translate economic interest into public health narratives. While governments focus on the measurement of costs and efficiency (cost-effectiveness), companies are focused on finding the threshold of effectiveness that supports their estimations of value. In terms of price setting, companies use cost-effectiveness for defining a border to limit some estimations of value (those based on cost-effectiveness) while at the same time crossing such limits by attributions of value based on the cost of knowledge and innovation.

Pharmaceutical companies have learnt the language of EBM, finding the threshold of effectiveness that supports their estimation of value. This article has shown different methods in which CEA is integrated into Gardasil's pricing strategy. CEA has raised HPV vaccines as a matter of interest for health authorities. Through cost-effectiveness modelling manufacturers have maximised the effectiveness of their products and have medicalized some conditions to extend their impact.

Prices are highly naturalised measurements of economic value. This paper presented some of the complexities and contingencies that are attached to price setting and the ways in which prices are entangled in different modes of calculation around HPV vaccines.

These different elements suggest that the formula that could represent HPV vaccines' pricing strategy in practice does not correspond either to cost (P=C+I) or to value based approaches (V=R+/-D). Such formulae could be much closer to a calculation in which cost-effectiveness defines a border to limit some estimations (State perspective) of value while at the same time shows a limit to be crossed by attributions of value based on the cost of knowledge and innovation. I would call such a strategy in which cost-effectiveness defines the minimum price and the quantification of innovation the added value and the maximum price of introduction, price-effectiveness. Its formula could be formalised as follows:

$$P= (V \geq SocV)+I$$

Price (P) is equal to the value of the vaccine (V) in a scenario of cost-effectiveness in which V is equal to or greater than the value of prevention from a societal perspective (SocV) plus the estimated value of innovation and profit (I). In this formula, price reflects a value relationship (V) that is inversely proportional to the costs of treatment. CEA should demonstrate that the cost of vaccines (CV) is less than the costs of the alternative to the vaccine (CA). If the cost of the vaccine is less, its value increases and therefore is more likely to have a higher price.

$$V' \propto \frac{1}{C} CV \leq CA$$

Valuation and market studies have taught us that prices are performative; they produce hierarchies and classifications of political objects such as countries and they constitute a way of quantifying their public value. This articles aims to contribute to the discussion about economics as engineering, showing the regime of valuation in healthcare that has surged around EBM. The analysis of pricing in the context of health policy renders visible the boundaries and the problems that the distinction between the market and the public sector brings. From the perspective of pharmaceutical companies, the public sector is characterised as a market, and different strategies of marketing and production–communication of value are developed for these companies to address the particularities that 'public sector' markets involve. Health economists have regarded CEA as a decisive factor in the success of pharmaceuticals within the contemporary frameworks of healthcare governance (Oshinowo et al. 2011). The success of the HPV vaccines market is linked to the capacity of companies to translate the value of the vaccine into the language of decision makers. However, cost-effectiveness is not enough to guarantee the success of a product. Manufacturers know that well. They have embedded CEA in a complex strategy to communicate/produce value through marketing, awareness campaigns and political lobbying.

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