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The Patent Buyout Price for Human Papilloma Virus (HPV) Vaccine and the Ratio of R&D Costs to the Patent Value

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Abstract

Human papillomavirus (HPV) is responsible for almost all of the 530,000 new cases of cervical cancer and approximately 266,000 deaths per year. HPV vaccination is an integral component of the World Health Organization's global strategy to fight the disease. However, high vaccine prices enforced through patent protection are limiting vaccine expansion, particularly in low- and middle-income countries. This raises the question of the patent buyout price for Merck's HPV vaccines (Gardasil-4 and 9), which hold 87% of the global HPV vaccine market. It also raises the question about the market power from patent protection, that we assess by estimating the ratio of R&D costs for Gardasil and its patent value. We estimate the patent buyout price for various groups of countries and in total. The estimated global Gardasil patent buyout price in 2020 is between US$ 15.33 – 18.32 billion (in 2018 US$), the estimated present discounted value of the profit stream for 2007-2028 amounts to US$ 22.29 – 33.08 billion, and the estimated total R&D cost is between US$ 1.10 – 1.21 billion. Thus, we arrive at a ratio of R&D costs to the patent value of the order of 3-5%, suggesting that patent protection provides Merck with extraordinarily strong market power.

Keywords: Human Papilloma Virus (HPV) vaccine; Market power; Patent buyout price; Patent value; R&D costs

JEL classification: I18; O30

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1. Introduction

By implying high vaccine prices, patent protection is considered one of the main factors limiting the expansion of vaccination in developing countries.[1] Pharmaceutical companies that develop and manufacture vaccines frequently face demands to lower vaccine prices in order to make them affordable to poorer countries. The typical counterargument is that lower prices could induce companies to withdraw certain vaccines from the market or reduce research and development (R&D) investments for new vaccines (Outterson, 2005; Light *et al.*, 2009).

There are two strategies to promote vaccine R&D: pull programmes that provide financial reward to companies that develop successful vaccines and push programmes that provide direct funds for research. Pull programmes include prizes, compulsory licensing and patent buyouts whereas push programmes include research grants and tax credit (Mueller-Langer, 2013). For lowering prices of pharmaceuticals, pull programmes that limit market power of pharmaceutical companies entail larger potential. Particularly, patent buyouts by government agencies have been suggested as a possible instrument to supply medicines at lower costs and make them affordable to poorer countries via licensing production to many competitors (Kremer, 1998). This raises the question of the patent buyout price a patent holder would be willing to accept for giving up patent protection, i.e. the present discounted value of incumbent's expected future profits over the remaining patent length.

In this study, we estimate the patent buyout price for two human papillomavirus (HPV) vaccines, Gardasil-4 and Gardasil-9,[2] from 2020 onwards, given the current and past pricing strategies by patent holder Merck.[3] We distinguish the patent buyout prices for low-income countries (LIC), middle-income countries (MIC), and high-income countries (HIC), particularly the U.S. Moreover, we estimate the global value of the Gardasil innovation at market entry and derive estimates of R&D costs. The ratio of R&D costs to the patent value is, in theory, the probability of the innovation under free entry of potential innovators in the market. Thus, an implausibly low estimated ratio would indicate that the

[1] Vaccines are biological preparations that confer protection against a range of infectious diseases. In addition to providing individual and community protection, vaccines also reduce the cost of treatment by decreasing disease burden. In African countries alone, nearly 3 million children die every year and approximately 24% of these deaths are caused by vaccine preventable diseases (Qazi *et al.*, 2015).

[2] Gardasil-4 was named one of the inventions of the year in 2006 by TIME magazine and has by far the largest sales for HPV vaccination. The patent gives Merck exclusive rights to manufacture, distribute and sell Gardasil-4 in the territories in which the patent is valid (Ooms *et al.*, 2014).

[3] It is important to include high-income countries (the classification of countries follows World Bank, 2019). Although patent buyouts for LIC and MIC would be most desirable and could in principle be relatively cheap in view of the low revenues in these countries (Outterson, 2005), focussing the patent buyout on these groups of countries may be infeasible. First, pharmaceutical companies may be reluctant to this solution because they fear (illegal) parallel imports or a black market for generic drugs. They may also fear public debate on (too) high prices in HIC, once local patent buyouts make high price-cost margins transparent elsewhere.

patent system gives Merck more market power than needed to serve the goal of providing proper innovation incentives.

Our focus on HPV vaccination derives, apart from data availability issues, from its importance for global health and the prevalence of HPV related diseases particularly in developing countries. HPV is a group that encompasses over 100 virus and 15 of them have been shown to be responsible for almost all cases of cervical cancer (Clifford *et al.*, 2005). Globally, around 630 million people are infected with HPV and half of women will have an infection by this virus in their lifetime (Merck, 2008). Sexually transmitted infection with HPV is the biggest risk factor for development of invasive cervical cancer (ICC) in females (McGraw and Ferrante, 2014). In addition, HPV induced anogenital cancers and genital warts in males are major causes of morbidity and represent a significant health burden. Furthermore, HPV infection has been associated with cancers of the anus, vulva, vagina and penis (Frisch and Goodman, 2000; Insinga *et al.*, 2005).[4]

On average, there are 530,000 new cases of cervical cancer and approximately 266,000 deaths per year with the highest incidence in developing nations where HPV vaccine coverage is low (UNICEF, 2018). In developing countries, cervical cancer is the largest cause of HPV related deaths with an estimated incidence of 40 out of 100,000. In sub-Saharan Africa, approximately 70,722 new cases of ICC are reported every year, the highest in the world (Louie *et al.*, 2009). By 2030 cervical cancer is projected to cause around 474,000 deaths in women annually and the vast majority (95%) of these deaths are expected to be in LIC and MIC (Saxena *et al.*, 2012).[5]

Vaccine and drug R&D is divided in two stages, pre clinical (*in vitro* and *in vivo* studies) and clinical trials (phase I-III). Most of the pre-clinical development of Gardasil-4 was performed by the National Cancer Institute (NCI), Georgetown University and University of Queensland who were the first to developed virus-like particle (VLP) technology used in the vaccine in the early 1990s (Padmanabhan *et al.*, 2010). Merck later acquired the licenses and took the then vaccine candidate to clinical testing (Padmanabhan *et al.*, 2010).

To estimate the R&D costs, we identified each clinical trial sponsored by Merck on www.clinicaltrial.gov and calculated the costs based on previous estimations per subject (Light *et al.*, 2009), clinical trial site and study (Sertkaya *et al.*, 2016). The HPV vaccine patent buyout estimation is

[4] In cohort of homosexual males aged 16–20 years 39% tested positive for HPV DNA. Within the subgroup 23% tested positive for the HPV subtypes that are covered by Gardasil-4 vaccine (6, 11, 16 and 18) (Zou *et al.*, 2014). In another study in South Africa HPV11 was detected in 80% of penile precancerous lesions, HPV16 was detected in 62.9% of cancerous lesions and some of the lesions were positive for various HPV types (Lebelo *et al.*, 2014).

[5] In the developed world, by contrast, there has been a steady decline in incidence and mortality caused by cervical cancer. For instance, in the U.S. and UK there was a 70% decrease in the mortality due to cervical cancer between the last quarter of the 20th century and the first decade of the 21st century. The average incidence of cervical cancer, age-adjusted, is 10 out of 100000 per year (McGraw and Ferrante, 2014).

based on data for costs of materials, labour costs, capital costs and overhead costs provided by Clendinen *et al.* (2016). Moreover, we employ data for sales and prices in different markets to come up with regional profit estimates which we extrapolate in the future for the remaining patent lenghts.

Our estimated global patent buyout in 2020 for Gardasil vaccines is between US$ 15.33 – 18.32 billion in 2018 U.S.$, depending on assumed real annual return to investment in alternative uses and cost estimates. The patent value, from market entry to patent expiry, we estimate between US$ 22.29 – 33.08 billion. These high values reflect our findings of high price-cost margins (mark-up factors) which could be around 100 for the U.S. and China and still well above 10 in MIC. For R&D costs for both Gardasil vaccines, including an additional 15% as costs of capital, we come up with an estimated range between US$ 1.1 – 1.21 billion. The latter two estimates imply a ratio of R&D costs and the patent value between 3% and 5%. This suggests that if there were free entry into R&D, the innovation probability would be astonishingly low.

Galasso et al. (2016) proposed an R&D incentive-compatible mechanism for designing a patent-buyout. However, the mechanism presumes that prices can be manipulated to infer the demand function for a pharmaceutical, mitigating applicability (Galasso *et al.*, 2016). Beyond the specific vaccine for HPV we consider, our suggested methodology could generally be employed to estimate patent buyout prices and to inform policy makers on the profits from innovations in relation to R&D costs, with possible implications for price negotiations and adjustment in the patent system. To date, most studies that estimate R&D costs relied on self-reported data from confidential pharmaceutical companies and industry experts that are impossible to assess for accuracy, representativeness, or sensitivity to outliers, arriving at estimates for drug development in the range of US$ 161 million to US$ 1.8 billion (Morgan *et al.*, 2011).[6] Furthermore, many pharmaceutical companies receive public and non-profit funds that confound the estimates on the companies' own R&D investments (Morgan *et al.*, 2011).

The structure of the paper is as follows. Section 2 discusses the use of vaccines for HPV, who manufactures them, sales revenues, HPV patents, and the benefit of HPV vaccines patent buyouts. Section 3 presents the methodology. Section 4 shows estimates of prices, doses sold, and variable manufacturing costs. Section 5 presents the estimation of operating profits, fixed costs and the total patent value of the main HPV vaccine, Gardasil-4. Section 6 presents estimates for R&D costs and relates them to the patent value for Gardasil. The last section concludes.

[6] Light et al. (2009) calculated the costs of the R&D of Rotavirus vaccine and found that the pharmaceutical companies responsible for the development of these vaccines declared higher R&D costs in order to charge higher prices.

2. Background: Vaccines for HPV and Patent Applications

Fifteen HPV types have been shown to have oncogenic potential: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82. One of the challenges to create a vaccine and treatment for HPV is the fact that an individual can be infected by more than one HPV type (Choi *et al.*, 2012). Globally, HPV 16 and 18 are responsible for approximately 70% of all cases of cervical cancer. HPV type 16 causes mainly squamous cell carcinoma whereas HPV 18 causes the less aggressive adenocarcinoma (Bosch *et al.*, 2008). In Africa, HPV 16 and 18 are responsible for 43.7-90.2% of the ICC cases (Louie *et al.*, 2009).

The standard treatments for early and advanced cervical cancer are surgery, chemotherapy and treatment with anti-viral agents such as cisplatin. However, none of these approaches are highly effective and there is a high rate of recurrent disease (Diaz-Padilla *et al.*, 2013). The costs of screening, treating and follow up are expensive for developed economies and almost prohibitive for developing economies that lack financial resources, expertise and infrastructure to provide effective measures.[7]

In individuals already infected with HPV the prophylactic vaccine is useless. The reason is that prophylactic vaccines only block entry of HPV into cervical epithelial cells whereas therapeutic vaccines target the intracellular virus and induce a T-cell-based immunity leading to killer T-cells eliminating HPV-infected cells (McKee *et al.*, 2015). By contrast, therapeutic vaccines have the potential for an immediate effect in reducing the incidence of HPV infection. Currently there are two promising therapeutic vaccines candidates that target HPVE6 and E7 proteins which combine newly developed adjuvants, delivery vectors and knowledge of the tumour microenvironment (McKee *et al.*, 2015). However, it may take considerable time until effective HPV therapeutic vaccines reach the market (Ma *et al.*, 2010).

2.1 Prophylactic HPV Vaccines

The two most widely used prophylactic vaccines in the market are Gardasil-4 (Merck, NJ, USA) and Cervarix (GlaxoSmithKline-GSK, Middlesex, UK). Gardasil-4 was approved for both U.S. and European markets in September 2006 whereas Cervarix was approved in September 2007 (EMA, 2009; McKee *et al.*, 2015). They target HPV L1 major capsid protein that assemble to form VLPs with a morphology similar to the HPV native virions and generate robust antibody responses against the targeted HPV

[7] In the U.S., the cost of treating and preventing all HPV associated diseases such as cervical and other HPV induced cancers (anal, vaginal, vulvar and penile), oropharyngeal cancer, genital warts and recurrent respiratory papillomatosis was estimated to be around US$8.0 billion in 2010. The breakdown of this costs is as follows: US$6.6 billion cervical cancer screening and follow-up, US$1.0 billion for treatment of HPV related cancer (US$ 400 million for cervical cancer and US$ 300 million for oropharyngeal cancer), US$ 300 million for treatment of genital warts and US$ 200 million for recurrent respiratory papillomatosis (RRP) (Chesson *et al.*, 2012).

types (Ma *et al.*, 2010). Both vaccines contain VLPs for HPV 16 and 18, which cause cervical cancer, but Gardasil-4 also has VLPs for HPV 6 and 11, which cause benign genital warts. The U.S. Food and Drug Administration (FDA) approved Gardasil-4 for immunization against HPV in males and females aged between 9-26 years whereas Cervarix is approved only for females aged between 10-25 years (Ma *et al.*, 2010).[8] Merck introduced a new HPV vaccine, Gardasil-9, in the U.S. and Europe in 2014 and 2015 respectively. In addition to the four HPV types covered in Gardasil-4, the new vaccine also provides protection against HPV types 31, 33, 45, 52 and 58 (Merck, 2018).

Table 1. Global revenue of Gardasil and Cervarix from 2006-2018.

	Gardasil (in million US$)*	**Cervarix (in million US$)****
2006	234.8	-
2007	1,480.6	20.1
2008	1,402.8	248.75
2009	1,118.4	306.68
2010	988	367.84
2011	1,209	814.66
2012	1,631	423.9
2013	1,831	261.44
2014	1,738	202.96
2015	1,908	137.28
2016	2,173	106.92
2017	2,308	172.86
2018	3,151	180.78

* Includes sales of Gardasil-4 and Gardasil-9. From 2016 onwards, only Gardasil-9 was sold in the U.S. (CDC, 2018b, 2018a). ** Original revenues are in Great Britain Pound (£). We used the exchange rate of the respective year on July 2 (MacroTrends, 2019) to calculate the revenue in US$.

Sources: (Merck, 2008, 2009, 2012, 2015, 2017, 2018) for Gardasil, (GSK, 2008, 2011, 2014, 2017, 2018) for Cerverix.

Table 1 shows global revenues of Gardasil and Cervarix between 2006 and 2018. We derive that Gardasil has clearly dominated with an average market share of 87% in the period 2007-2018, which is the main reason we will focus on Gardasil (in addition to being effective against more HPV types).

[8] Both vaccines were found to be safe and immunogenic in clinical trials and were not associated with increased risk of autoimmune disorder (Macartney *et al.*, no date; Moreira *et al.*, 2011; Luna *et al.*, 2013; Grimaldi-Bensouda *et al.*, 2014). In terms of inducing cross reactive antibodies, Cervarix was found to provide significant protection against HPV types 31, 33, 45 and 51 (which account to 10-15% of the cervical cancer cases) whereas Gardasil-4 only provided cross protection against HPV type 31, 33 and 55 (Schiller *et al.*, 2012; Wheeler *et al.*, 2012). The geometric mean antibody titres against HPV type 31, 33 and 55 induced by Gardasil-4 and Cervarix were comparable (Toft *et al.*, 2014).

Vaccination is an integral part of the WHO global strategy to combat HPV infections and related diseases (Merck, 2017; UNICEF, 2018). According to WHO recommendations, girls aged 9-14 years should receive two doses of Gardasil-4 whereas older age groups receive three doses (UNICEF, 2018). It is too early to assess the impact of Gardasil-4 and Cervarix vaccination on prevalence of ICC because progress from HPV infection to cancer is very slow. One strategy commonly used to evaluate the impact of HPV vaccination is assessing the prevalence of HPV infection or genital warts in the general population (McKee *et al.*, 2015). When given at recommended doses, Gardasil-4 has been shown to induce antibody protection against HPV types covered by the vaccine for at least 5 years (Garland *et al.*, 2007; Choi *et al.*, 2012). In males aged 16-26 years, Gardasil-4 has been shown to provide 90.4% efficacy against lesions related to HPV types covered by the vaccine (Giuliano *et al.*, 2011).[9]

It is estimated that 70-80% of females in pre-pubertal age have to be vaccinated in order to achieve heard immunity (McGraw and Ferrante, 2014). Although HPV vaccination has been introduced in 81 countries, the high costs of the vaccine and the fact that it requires the delivery of two or three doses over a period of 6 months makes it a significant financial and structural burden to most countries in the world. For this reason, most LIC and MIC struggle to maintain HPV vaccination without the aid of other countries and global organizations such as the WHO, the Global Vaccine Alliance (GAVI), United Nations International Children's Emergency Fund (UNICEF) and Pan American Health Organization (PAHO) (McKee *et al.*, 2015).

Despite negotiating much lower prices for LIC and MIC countries, GAVI and other global organizations involved in vaccination have repeatedly complained that the prices remain high and this has been one of the major factors limiting the expansion of HPV vaccination. In these countries, it has been estimated that HPV vaccination has the potential to reduce the lifetime risk of cervical cancer by 31-60% (Goldie *et al.*, 2008).

2.2 HPV Vaccine Patents

Academic institutes in the U.S. and Australia first developed the technology employed in the VLP-based vaccines in the early 1990s. Merck and GSK then improved on the original invention and performed

[9] In Denmark, a study recorded a 67% drop in anogenital warts in females and 50% drop in males vaccinated against HPV. Chlamydia infection level remained the same, strongly suggesting that the reduction in HPV infection was due to vaccination and not change in sexual behavior (Sandø *et al.*, 2014). In Australia, one of the first country to introduce government funded HPV vaccination program, there was a 92% drop in diagnosis of genital warts in females under 21 between 2007-2011 (McKee *et al.*, 2015). Another study in Australia has used surrogate markers to give an indication of the possible impact of vaccination on cervical cancer. It evaluated a cohort of 14,085 unvaccinated and 24,871 vaccinated women within 5 years of the implementation of the vaccination program. It found that the subjects in the unvaccinated cohort presented significantly higher frequency of histological and cytological high-grade abnormalities (Gertig *et al.*, 2013).

the subsequent steps required to bring the vaccine to the market (Padmanabhan *et al.*, 2010). Merck's Gardasil-4, the first VLP based vaccine, was patented in the U.S. in 1998 and introduced in the market in 2006 (Castro *et al.*, 2017). Between the first patent approval and 2010, 81 HPV vaccine related patents were granted in the U.S. with Merck leading the way with 24 granted patents (Padmanabhan *et al.*, 2010).[10]

Table 2. Patent expiry year of Gardasil-4 and Gardasil-9 in the EU and North America.

	Gardasil-4	**Gardasil-9**
U.S.	2028	2028
Canada	2020	2025
EU	2021	2030*

* The European Union (EU) may give an additional six months of paediatric market exclusivity attached to a product's Supplementary Protection Certificate (SPC) (Merck, 2018).

Source: (Health Canada, 2018; Merck, 2018).

Typically patents are granted for 20 years but often companies successfully apply for extension up to five years (Lakdawalla, 2018). Under the agreement on trade-related aspects of intellectual property rights (TRIPS), administered by the World Trade Organization (WTO) and enforced in 1995, member countries with an industry capable of manufacturing vaccines must enforce patent protection of medicines and biological products (Chandrasekharan *et al.*, 2015). However, under the agreement, the least-developed countries (UN, 2018) are not obliged to provide patent protection in general until 2021, and on medicines (including vaccines) specifically until 2033 (MSF, 2017).

Brazil, India and China have a large generic pharmaceutical industry supplying 64% of vaccines purchase by UNICEF and 43% of vaccines procured by GAVI (Padmanabhan *et al.*, 2010). In addition to manufacturing generic vaccines, these countries are also capable of developing HPV vaccines themselves (Padmanabhan *et al.*, 2010). A common strategy used in the pharmaceutical industry to limit competition from Brazil, India and China is to apply for patents in these countries. There has been over 100 HPV vaccine related patent applications with GSK and Merck, the two companies that dominate the HPV vaccine market, having by far the highest number of patent applications (Chandrasekharan *et al.*, 2015).

[10] Given the wide coverage and complexity of patents held by Merck and GSK on HPV vaccine technology, both companies cross-licensed their respective intellectual property (IP) holdings to each other in 2005 to enable them to have access to the technologies they possess in HPV vaccine R&D and manufacturing (MSF, 2017).

There is no centralized database to obtain information about the status of the various patents related to a particular vaccine in different countries/regions. For Table 2, we gathered patent expiry years from Merck's annual reports. For simplicity, we focus on patent buyout prices for all country groups and total patent values until 2028.

2.3. The Benefit of Patent Buyouts

WHO has launched a global effort to eliminate cervical cancer promoting introduction of HPV vaccination in all countries. The demand is expected to approach 100 million doses per year over the next decade. The current suppliers will not be capable to meet the demand meaning that new manufacturers will need to enter the market (WHO, 2018).

In line with the global WHO effort, 48 GAVI-supported countries are expected to introduce multi-age cohort HPV vaccination in the coming 10 years (WHO, 2018). The introduction of HPV vaccination in China, India and Indonesia adds significantly to global demand. The WHO estimates that from 2023 the demand for HPV vaccines will exceed production capacity (GAVI, 2017).

Under current production capacity it will be challenging to implement gender-neutral and multi-age cohort vaccination, as recommended by the WHO, not only because of the limited production capacity of the current approved manufacturers but also the high prices of HPV vaccines that are prohibitive to GAVI and PAHO supported LIC and MIC as well as in non-supported MIC. In fact, although 81 countries have included HPV vaccination in their routine immunization programmes, many LIC and MIC are struggling to introduce or maintain the vaccine in their programmes because of its high costs. To date, 74% of the 81 countries that have introduced the HPV vaccination self-procure the vaccines (WHO, 2018).

This suggests the entrance of new manufacturers and vaccines as being crucial to ensure sufficient supply and lower HPV vaccine prices, thus increasing economic efficiency. Patent buyout for the market leader Gardasil-4 and Gardasil-9 would allow fast entry of competitors.[11]

[11] It will take considerable time until new HPV vaccines from rival companies reach the market. For instance, the bivalent vaccines from Innovax and Shanghai Zerun Biotech are in phase III clinical trials whereas the quadrivalent HPV vaccine from Serum Institute of India just entered Phase II (WHO, 2018). These vaccines are yet to be tested in real world conditions.

3. Methodology

3.1 Patent buyout price

Our first goal is to estimate the patent buyout price for the vaccine Gardasil in year $\underline{T} = 2020$, in current (2018) US$.

To calculate the time path of operating profits, we need estimates for variable and fixed production costs, in addition to prices. We assume that the variable production cost per unit (dose) is independent of the number of produced doses such that total variable costs are proportional to the units sold. They consist of

- manufacturing costs for materials,
- user costs of capital (equipment and building),
- costs for manufacturing labour (manufacturing operators and quality assurance and quality control operators), and
- costs for filling and packaging (staff and material).

Fixed production costs are calculated for each single facility and consist of

- overhead labour costs for managing and supervising the manufacturing process of the facility,
- labour costs for maintenance of the facility and all of its equipment.

Total fixed costs are the fixed costs of each facility summed up.
Notably, *ex ante* costs like R&D expenditures that are sunk at the production stage are not part of the fixed production cost.[12]

Our data will provide us with recent estimates for the cost components. We use the U.S. price index published by the Federal Reserve to deflate all prices and costs to its 2018 value.

Unlike the number of does sold and consumer prices, we assume that both variable unit costs and fixed costs are time-invariant in *real* terms. We index the country (group) in which Gardasil is sold by $j \in \{1,2,\dots,J\}$ and denote the time horizon by T (year 2028 in our application). We use information about the time paths of the predicted future number of doses sold at the regional level, $\{y_{jt}\}_{t=\underline{T}}^{T}$. In year *t*, real operating profits (in 2018 dollars) from country group *j* are then given by

$$\pi_{jt} = (p_{jt} - c)y_{jt}, \tag{1}$$

where c denote real variable costs per unit and p_{jt} denotes real sales prices in region *j* and year *t*. We assume that future real sales prices stay at the level we observe last.

[12] This also applies to marketing costs.

Based on (1), we can then estimate the patent buyout price in real dollars, v_j, in region j as the remaining present discounted value of the patent from period $\underline{T}$ onwards of the profit stream until the patent effectively ends in country group j:

$$v_j(\underline{T}) \coloneqq \sum_{t=\underline{T}}^{T} \frac{\pi_{jt}}{(1+r)^{t-\underline{T}}} \tag{2}$$

where r is the real annual return to investment in alternative uses (like deposits in banks, equity holding, government bonds, etc). We present our estimates for the annual real interest rate r in the typical range of 3-7%.

We will also report global patent buyout prices in year $\underline{T}$ for the considered regions as a whole:

$$V(\underline{T}) \coloneqq \sum_{j=1}^{J} v_j(\underline{T}) - F \qquad - \tag{3}$$

where F denotes the total real fixed costs of all production facilities. We assume that c and F are the same for Gardasil-4 and Gardasil-9.

3.2 Implied Probability of Innovation Under Free Market Entry

We also aim to estimate the value of an innovation from the perspective of the date introduced in the market and compare it with R&D costs. Denote the first full year in which the Gardasil was sold by $s = 2007$, i.e. the total patent value is given by $V(s)$.[13] Calculating $V(s)$ requires also the observations for the past number of doses and prices for all country groups j (i.e. in years $t \in \{s, s+1, \dots, \underline{T}-1\}$), in addition to the information employed to calculate $V(\underline{T})$ given in eq. (3).

If the market for innovations were characterized by free entry, total expected profits would equal zero. That is, the expected value of an innovation (accounting for a potentially high risk of R&D failure) would equal R&D costs. Formally, the free entry equilibrium condition (zero-profit condition) reads as

$$\mu \cdot V(s) = R\&Dcosts, \tag{4}$$

where μ denotes the probability of a successful innovation. Recall that Gardasil-9 was an improvement of Gardasil-4, the first HPV vaccine approved by the FDA (Tomljenovic and Shaw, 2012). Gardasil-4 and Gardasil-9 are typically not sold in parallel within the same region. Thus, we sum up both the profits from both Gardasil-4 and Gardasil-9 and add up the R&D costs for both when applying eq. (4). Given our estimates of R&D costs and the innovation value, we obtain $\mu = \frac{R\&D\ costs}{V(s)}$ as the theoretical probability of a successful innovation under the free entry assumption. If μ were deemed too low, then we would have indication of excessive market power.

[13] We neglect sales in year 2006, as Gardasil-4 was only sold in the U.S. after its approval in September 2006 and we do not have price information.

4. Data for Operating Profit Estimates

4.1. HPV Vaccine Prices

When Gardasil was first released in the U.S. market it was sold at US$ 96.75 per dose to Centers for Disease Control (CDC) funded programs and US$ 120.5 per dose to the private sector making it the most expensive vaccine at the time (Table 3) (Nguyen *et al.*, 2011; CDC, 2018a). In 2018, it was sold at a price of US$144.2 and US$ 217.1 to CDC and the private sector respectively (CDC, 2018a). Since the data about the number of doses sold to CDC and the private sector is not available we assume in Table 3 that each corresponds to 50% of the total doses sold and calculate the U.S. price as the simple mean of the price charged to the two groups. Since we have prices from various years, we converted all prices to 2018 US$, using the U.S. consumer price index (Federal Reserve Bank, 2018).[14]

Table 3. Gardasil prices* per dose in the U.S. from 2007-2018.

Year	CDC (in current US$)	Private Sector (in current US$)	Average price (in current US$)	Price in 2018 US$**
2007	96.75	120.50	108.63	131.55
2008	100.59	125.29	112.94	131.72
2009	105.58	130.27	117.93	138.03
2010	108.72	130.27	119.50	137.61
2011	95.75	130.27	113.01	126.16
2012	98.60	135.45	117.03	127.99
2013	107.16	135.45	121.30	130.76
2014	121.03	141.38	131.21	139.17
2015	121.03	160.17	140.60	148.96
2016	119.04	193.63	156.34	163.57
2017	116.22	204.87	160.55	164.47
2018	144.18	217.11	180.64	180.64

* In 2016, Gardasil-4 was replaced by Gardasil-9. ** Deflated by the price index (PI) as given in Table B.1.

Source: (CDC, 2018a) and own calculations.

Globally the prices of HPV vaccines vary greatly depending on procurement agreement and countries' income (UNICEF, 2018). Merck and GSK have agreements with organizations such as GAVI (mediates purchase of vaccine to developing countries in Africa and Asia) and PAHO (mediates vaccine purchase to LIC and MIC in South and Central America) (GAVI, 2018; PAHO, 2019) . Table 4 displays the median price per dose for Gardasil-4 and Gardasil-9 in the year 2016 and the one in 2018 US$ for various

[14] See Supplementary Material (Table B.1).

(groups of) countries. We see that although median prices are much higher in HIC, the vaccines are particularly expensive in China.

Table 4. Prices of Gardasil-4 and Gardasil-9 in different countries and country groups (median prices within the groups of HIC and MIC), excluding the U.S, 2016.

	2016, in curent US$		**In 2018 US$***	
	Gardasil-4	**Gardasil-9**	**Gardasil-4**	**Gardasil-9**
HIC (excl. the U.S.)	44.12	91.00	45.96	94.79
MIC	19.70		20.52	
GAVI	4.50		4.69	
India	6.90		7.19	
Indonesia	14.76		15.38	
China	120.00	153.00	125.00	159.38

* Prices for 2016 are deflated by PI=0.96 (Table B.1).

Sources: HIC, MIC, GAVI, PAHO (UNICEF, 2018); India (Sabeena *et al.*, 2018); Indonesia (Setiawan *et al.*, 2016); China (Yin, 2017; Cheung and Zhang, 2018) and own calculations.

4.2 Number of Doses Sold

To calculate operating profits for a year *t* as given in eq. (1), we also need an estimate the number of doses y_{jt} in each country group *j*. Currently there are no publicly available data on the number of doses of Gardasil sold globally. GAVI (2017), through its own databases and interviews with stakeholders (i.e. national vaccination programme managers, industry leaders and experts), estimated the number of HPV doses sold between 2006-2017 by country group and forecasted quantities for 2018-2027. Unfortunately, for the past, only the total number of doses per year for HIC as a whole is available, which is problematic as we see by comparing Table 3 and 4 that prices are much higher in the U.S. Thus, one challenge is to derive the breakdown of the total number of units between the U.S. and other HIC for the period 2007-2017 (recall that we aim to calculate the patent value since 2007).

We infer these figures as follows: we use the available Gardasil revenue information for the U.S. (Merck, 2019) in 2015-2017 to calculate in Table 5a its average market share during that period. It amounts to 76.46%. Then we assume U.S. the market share was the same also in 2007-2014 and infer the Gardasil-4 sales revenue for the U.S. market in this period by using global revenues as given in Table 1. Finally, we divide the U.S. sales revenues by the information on the nominal (average) price in Table 3.

Table 5a. U.S. market share, 2015-2017.

Year	U.S. revenue (in million US$)	Total revenue (in million US$)	U.S. market share (%)
2015	1,520	1,908	79.66
2016	1,780	2,173	81.91
2017	1,565	2,308	67.81
Average U.S. market share			76.46

Source: (Merck, 2019)

Table 5b. Total Gardasil sales revenues, its estimated composition (U.S. vs. non-U.S.) and estimated number of doses sold in the U.S., 2007-2017.

	Revenue (in million US$)			U.S.	
Year	**U.S.***	**Non-U.S. ***	**Total**	**Nominal U.S. price/dose****	**Number of doses sold in the U.S. (in millions)**
2007	1,132.07	348.53	1,480.60	108.63	10.42
2008	1,072.58	330.22	1,402.80	112.94	9.50
2009	855.13	263.27	1,118.40	117.93	7.25
2010	755.42	232.58	988	119.5	6.32
2011	924.40	284.60	1,209	113.01	8.18
2012	1,247.06	383.94	1,631	117.03	10.66
2013	1,399.98	431.02	1,831	121.30	11.54
2014	1,328.87	409.13	1,738	131.21	10.13
2015	1,520	388	1,908	140.60	10.81
2016	1,780	393	2,173	156.34	11.39
2017	1,565	743	2,308	160.55	9.75

* For 2007-2014 we assumed the U.S. (non-U.S.) market share corresponds to 76.46% (23.54%) of the global Gardasil revenue market, as calculated in Table 5a, using the figure for total revenues. ** The column restates the average price from Table 3.

Source: (GAVI, 2017) and own calculations.

Table 5c. Nominal prices and number of doses in HIC excluding the U.S., 2007-2009.

Year	Revenue (in million US$)	Nominal price/dose in other HIC (in US$)*	Number of doses sold in other HIC (in millions)**
2007	348.53	37.95	9.18
2008	330.22	39.41	8.38
2009	263.27	39.27	6.70

* Calculated from Table 4 and PI in Table B.1. ** We used the revenue information for non-U.S. countries from Table 5b.

Table 5b displays the number of Gardasil doses sold in the U.S. derived by that procedure (in addition to sales revenues derived as intermediate steps). Table 5c uses the breakdown of revenues together with the information on prices in Table 4 to infer the number of units sold in 2007-2009 in HIC other than the U.S., using the information by Merck that Gardasil has only been sold in HIC in that period. The price estimate is constructed by multiplying the real Gardasil-4 price of 45.96 US$ (in 2018 US$) shown in Table 4 by its PI in the respective year from Table B.1.

Table 6a. Number of Gardasil doses sold in different countries and country groups between 2010-2017 and forecasted quantities until 2027.

Year	Number of doses (in millions)							
	HIC total	U.S.**	Other HIC***	MIC	GAVI	India/Indonesia	China	Total
2010	15.66	6.32	9.34	6.09	0	0	0	**21.75**
2011	20.88	8.18	12.70	11.31	0	0	0	**32.19**
2012	18.27	10.66	7.61	13.92	0	0	0	**32.19**
2013	17.4	11.54	5.86	13.92	0.87	0	0	**32.19**
2014	15.23	10.13	5.10	11.31	0.87	0	0	**27.41**
2015	14.79	10.81	3.98	9.57	1.74	0	0	**26.10**
2016	15.66	11.39	4.27	9.57	2.61	0.87	0	**28.71**
2017	15.66	9.75	5.91	9.57	1.74	0.87	0	**27.84**
Subtotal	**133.5**	**78.77**	**54.77**	**85.26**	**7.83**	**1.74**	**0**	**228.38**
2018*	14.79	8.84	5.95	10.44	5.22	0.87	0	**31.32**
2019*	15.23	9.10	6.12	12.18	23.49	0.87	0	**51.77**
2020*	16.53	9.88	6.65	13.05	34.8	0.87	0	**65.25**
2021*	15.66	9.36	6.30	13.05	26.97	13.92	0	**69.60**
2022*	14.79	8.84	5.95	13.05	28.71	25.23	0.87	**82.65**
2023*	13.92	8.32	5.60	13.05	31.32	23.49	2.61	**84.39**
2024*	13.05	7.80	5.25	13.92	21.75	24.36	3.48	**76.56**
2025*	12.18	7.28	4.90	14.79	27.84	21.75	3.48	**80.04**
2026*	12.18	7.28	4.90	14.79	26.1	20.01	4.35	**77.43**
2027*	12.18	7.28	4.90	14.79	25.23	18.27	6.09	**76.56**
Subtotal	**140.5**	**84.02**	**56.48**	**133.11**	**251.43**	**149.64**	**20.88**	**695.57**

* Assuming that the number doses sold in the U.S. from 2018-2027 corresponds to 59.8% of the total number of doses sold in HIC markets (see Table 6b). ** For 2010-2017, see Table 5b. *** Implied by subtracting the number for HIC total and the U.S.

Source: (GAVI, 2017) and own calculations.

For the period 2010-2017 we can again use our estimates for the number of doses in the U.S. to infer those of other HIC. The results are given in Table 6a. For the period 2018-2027, we assume that the

share among HIC of the number of doses sold in the U.S. from 2018-2027 corresponds to its average share in period 2010-2017. According to Table 6b, on average, 59.8% of the total number of doses sold in HIC markets are sold in the U.S.

Table 6b. U.S. share of total number of doses sold in HIC, 2010-2017.

Year	Number of doses sold in all HIC (in millions)	Number of doses sold in U.S. (in millions)*	U.S. market share (in %)
2010	15.66	6.32	40.4
2011	20.88	8.18	39.2
2012	18.27	10.66	58.3
2013	17.4	11.54	66.3
2014	15.23	10.13	66.5
2015	14.79	10.81	73.1
2016	15.66	11.39	72.7
2017	15.66	9.75	62.2
Average U.S. market share (in %)			**59.8**

* See Table 5b.

Source: (GAVI, 2017) and own calculations.

For the other regions, the past and forecasted number of Gardasil doses sold have been directly provided (GAVI, 2017). They are also displayed in Table 6a. The biggest factor that will drive the increase in global demand of HPV vaccine is the introduction of HPV vaccination in China, India and Indonesia (three of the four most populous countries in the world). These countries are expected to represent approximately 1/3 of the global market by 2030 (GAVI, 2017; WHO, 2018). China, India and Indonesia delayed the introduction of Gardasil-4 and Gardasil-9 in their public health programmes due to concerns over safety, effectiveness of the vaccine across different age groups and price. China approved the introduction of Gardasil-4 and Gardasil-9 in 2017 and 2018 respectively, Indonesia introduced Gardasil-4 in late 2015 and India did so in 2018 (Kosen *et al.*, 2017; Das, 2018; Hongyu, 2018; Sagonowsky, 2018).

4.3 Variable Costs for Manufacturing Gardasil

As outlined in section 3, we distinguish variable and fixed manufacturing costs.[15] Variable costs consist of annual costs for labour, per-batch costs for raw materials, filling and packaging the vaccine, and capital costs. Fixed costs include management and supervisor overhead costs and fixed costs required

[15] In line with our methodology, most studies do not include the costs of R&D, marketing, general administration and legal services in the estimation of manufacturing costs (Mahoney, 1990; Smith *et al.*, 2011; Mahoney *et al.*, 2012).

to fulfil 'Good Manufacturing Practices' (GMP) guidelines, i.e. "factory and administrative overhead" (Clendinen *et al.*, 2016).

Annualized capital costs consist of building and equipment costs, where equipment represents around one-third of these costs. We follow the procedure to assume a 5% real (no-inflation) discount rate, 10 years of useful life for the equipment and 25 years of useful life for the building (Mahoney *et al.*, 2012; Clendinen *et al.*, 2016). For Gardasil-4, as shown in Table 7a, one quarter of the US$1 billion (in 2014 US$) spent by Merck in building its manufacturing complex in Durham (North Carolina), was used as the high estimate for total variable capital costs; and a 40% discount, or $150 million for the low estimate (Clendinen *et al.*, 2016). Based on the total number of doses between 2010-2017 derived in Table 6a, Table 7b displays the number of doses of Gardasil-4 that can be manufactured annually with the total investment for building and equipment shown in Table 7a.

Table 7a. Total capital (building and equipment) costs for Gardasil-4 (in 2014 US$).

	Low Estimate	**High Estimate**
Investment (in million US$)		
Building cost	100	166.7
Equipment cost	50	83.3
Total investment in building and equipment	150	250
Cost of capital (in million US$)		
Annualized capital cost - Building*	6.8	11.3
Annualized capital cost - Equipment*	6.2	10.3
Total annualized capital cost*	13	21.6

* Assuming 5% real (no inflation) discount rate; useful life 10 years for equipment and 25 years for building; range of costs shown to reflect uncertainty in estimates.

Source: (Clendinen *et al.*, 2016).

Table 7b. Number of doses of Gardasil-4 manufactured**.**

		Number of doses (in millions)
A	Total number of doses between 2010-2017*	228.375
B	Average number of doses per year	28.546875

* See Table 6a.

Table 7c uses the information in Tables 7a and 7b to calculate the range of variable capital costs per one million doses of Gardasil-4.

Table 7c. Estimated variable capital costs (per year) for manufacturing 1 million doses of Gardasil-4**.**

	Low estimate (in US$)	High estimate (in US$)
Variable building cost (annualised capital cost/B)	238,204.71	395,840.18
Variable equipment cost (annualised capital cost/B)	217,186.64	360,810.07
Total variable capital cost for one million doses (in 2014 US$)	455,391.35	756,650.25
Total (in 2018 US$)*	428,067.87	711,251.24

* Deflated by PI from Table B.1.

Source: Own calculations based on Table 7a and 7b.

Table 8. Estimated cost of materials for producing 1 million doses of Gardasil-4.

Materials (units)*	**Package sold by life science companies**	**Price per package (US$)**	**Number of packages needed per million doses**	**Price for 1 million doses (US$)**
Yeast Media (kg)	0.02	100	7.11	35,532.47
Yeast Extract (kg)	1.00	300	88.83	26,649.35
Soy Protein (kg)	25.00	2,600	44.42	4,619.22
Magnesium Chloride (kg)	5.00	150	0.78	23.38
Thimerosal (g)	500.00	2,000	18.17	72.67
Glucose (kg)	2.50	250	88.83	8,883.12
Sodium Hydroxide (kg)	5.00	200	4.04	161.45
Galactose (kg)	5.00	700	177.66	24,872.73
PS--80 (kg)	25.00	360	10.09	145.37
Sodium Chloride (kg)	50.00	550	646.04	7,106.49
DTT (g)	100.00	1,000	38.96	389.61
Benzonase (ku)	25.00	180	299.81	2,158.60
MOPS (kg)	5.00	2,000	1.95	779.22
Ammonium sulfate (kg)	5.00	290	9.81	569.00
Microfiltration filters	1.00	10,000	0.10	974.03
Hollow--fiber membranes	1.00	9,000	0.10	876.62
PVDF—Millipore200 (3pk=3000L)	1.00	850	0.10	82.79
Poros 50HS beads 20x3ft (L)	10.00	22,500	34.77	78,222.56
Filling and packaging				310,000.00
High Estimate – Total listed retail prices (in 2013 US$)				**502,118.67**
High Estimate – Total listed retail prices (in 2018 US$)**				**539,912.55**
Low Estimate – Discounted at 40% (in 2018 US$)**				**323,947.53**

** Deflated by PI from Table B.1.

Source: (Clendinen *et al.*, 2016) and own calculations.

Merck's Gardasil-4 is produced from a combination of non-infectious and non-oncogenic VLPs that mimic the virion structure of the infectious particles of common HPV strains. It contains four VLPs of HPV type 6, 11, 16, and 18 each absorbed onto aluminium hydroxyphosphate sulphate (AAHS) adjuvant. All steps of the purification of L1 proteins are done individually for each protein (Clendinen *et al.*, 2016).

The manufacturing process has four steps: cultivation, extraction, purification type-specific VLPs from L1-recombinant producer cells, filling and packaging (Clendinen *et al.*, 2016). Table 8 displays the costs of materials (in 2013 US$) for one million doses of Gardasil-4 (the number of doses sold until May 2013). The materials are based on published papers from Merck on how the L1 proteins are produced and their costs are taken from the U.S. based life science and technology companies list prices in 2013. The variable materials cost for filling and packaging is US$ 310,000 for 1 million doses, being composed of the wholesale cost of the vial, cap and stopper (for single-dose packaging) at US$ 0.21 per dose plus secondary packaging materials at US$ 0.10 per dose (Clendinen *et al.*, 2016).

According to (Clendinen *et al.*, 2016), it takes 152 personnel across different functions (management, manufacturing, inspection and quality assurance) to manufacture two sets of batches or up to 30.8 million doses of Gardasil-4 in one year. Table 9 presents the range of salaries (low and high) per one million doses paid to operators involved in manufacturing, quality assurance and control plus staff costs for filling and packaging.

Table 9. Variable labour cost for producing 1 million doses of Gardasil-4.

Number of employees	**Personnel**	**Salary costs per employee for one million doses (US$)**		**Total salary costs (US$) per million doses**	
	Type	**Low**	**High**	**Low**	**High**
60	Manufacturing Operators	1,623.38	2,272.73	97,402.60	136,363.64
47	Quality Assurance and Quality Control Operators	1,623.38	2,272.73	76,298.70	106,818.18
34	Fill/Pack Staff	1,623.38	2,272.73	55,194.81	77,272.73
Total (in 2014 US$)				228,896.10	320,454.55
Total (in 2018 US$)*				243,506.49	340,909.09

** Deflated by PI from Table B.1.

Source: (Clendinen *et al.*, 2016) and own calculations.

In Table 10 we arrive at two estimates (low and high) of the total variable costs per dose, to manufacture one million doses of Gardasil, based on Tables 7c, 8 and 9. It is interesting to compare

them to prices as given in Tables 3 and 4 for the U.S. and other (groups of) countries. For instance, in 2016, even the high estimate would suggest a price-cost margin (mark-up factor) around 100 for the U.S. and China in the year 2016 and above 12 in MIC.

Table 10. Total variable costs for manufacturing 1 million Gardasil doses (in 2018 US$).

	Low estimate	**High estimate**
Material costs (per million doses)	323,947.53	539,912.55
Variable labour costs (per million doses)	243,506.49	340,909.09
Variable capital costs (per million doses)	428,067.87	711,251.24
Total variable costs per million doses	995,521.89	1,592,072.88
Total variable costs per dose	1.00	1.59

Source: Own calculations based on Tables 7c, 8 and 9.

5. Operating Profits, Fixed Costs and Patent Value

5.1. Operating Profits

Table 11 displays the profits in 2018 US$ by using eq. (1).[16] The data used to calculate profits were obtained from the estimations above: vaccine prices, p_{jt}, in the U.S. (Table 3) and other country groups (Table 4), number of doses sold, y_{jt} (Table 6a) and variable costs, c (Table 10). The estimations suggest a future reduction of the U.S. market share caused by the forecasted increasing demand for the vaccine in other regions particularly in China, India and Indonesia. Future profits tend to increase until 2027.

Table 11. Estimated past and future Gardasil operating profits in different countries and country groups, applying eq. (1). All values in million 2018 US$.

a) 2007-2009

	Estimation	**Year (in million 2018 US$)**		
		2007	**2008**	**2009**
U.S.	**High (US$)**	1,360.59	1,241.45	993.64
	Low (US$)	1,354.45	1,235.85	989.36
Other HIC	**High (US$)**	412.90	376.74	301.43
	Low (US$)	407.48	371.80	297.48
Total profit per year	**High (US$)**	1,773.49	1,618.19	1,295.07
	Low (US$)	1,761.93	1,607.64	1,286.84

[16] Calculations are displayed in Table B.2 of the Supplementary Material.

b) 2010-2019

	Estimation	Year (in million 2018 US$)									
		2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
U.S.	**High**	863.61	1,023.76	1,353.26	1,497.51	1,399.41	1,599.55	1,850.93	1,593.48	1,588.83	1,635.56
	Low	859.88	1,018.93	1,346.97	1,490.71	1,393.44	1,593.17	1,844.22	1,587.73	1,583.62	1,630.19
Other HIC	**High**	419.83	570.98	342.30	263.41	229.14	178.90	192.16	265.79	267.30	275.17
	Low	414.32	563.49	337.80	259.95	226.14	176.55	189.64	262.30	263.80	271.55
MIC	**High**	118.88	220.78	271.73	271.73	220.78	186.81	186.81	186.81	203.80	237.76
	Low	115.29	214.11	263.52	263.52	214.11	181.17	181.17	181.17	197.64	230.58
GAVI	**High**				3.21	3.21	6.42	9.62	6.42	19.25	86.62
	Low				2.69	2.69	5.39	8.08	5.39	16.17	72.76
Indonesia/ India	**High**							8.94	8.94	8.94	8.94
	Low							8.43	8.43	8.43	8.43
Profit per year (in million US$)	**High**	1,402.32	1,815.52	1,967.28	2,035.86	1,852.54	1,971.68	2,248.48	2,061.45	2,088.13	2,244.06
	Low	1,389.49	1,796.53	1,948.29	2,016.87	1,836.38	1,956.28	2,231.54	2,045.02	2,069.65	2,213.52

c) 2020-2027

	Estimation	Year (in million 2018 US$)							
		2020	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027**
U.S.	**High**	1,350.38	1,172.05	1,123.15	1,080.10	1,078.26	1,077.67	1,184.07	1,190.63
	Low	1,344.54	1,166.53	1,117.94	1,075.19	1,073.66	1,073.38	1,179.77	1,186.33
Other HIC	**High**	298.75	283.03	267.30	251.58	235.86	220.13	220.13	220.13
	Low	294.83	279.31	263.80	248.28	232.76	217.24	217.24	217.24
MIC	**High**	254.75	254.75	254.75	254.75	271.73	288.71	288.71	288.71
	Low	247.05	247.05	247.05	247.05	263.52	279.99	279.99	279.99
GAVI	**High**	128.33	99.45	105.87	115.49	80.20	102.66	96.24	93.04
	Low	107.79	83.54	88.93	97.01	67.37	86.23	80.84	78.15
Indonesia/ India	**High**	8.94	143.12	259.40	241.51	250.45	223.62	205.73	187.84
	Low	8.43	134.90	244.51	227.65	236.08	210.78	193.92	177.06
China	**High**			137.79	413.36	551.15	551.15	688.93	964.50
	Low			137.27	411.82	549.09	549.09	686.36	960.91
Profit per year (in million US$)	**High**	2,041.14	1,952.39	2,148.26	2,356.79	2,467.65	2,463.94	2,683.81	2,944.85
	Low	2,002.65	1,911.33	2,099.49	2,307.00	2,422.48	2,416.72	2,638.13	2,899.68

Source: Own calculations based on Tables 3, 4, 6a, 10.

5.2. Present Discounted Value of Operating Profits

Based on the profit information in Table 11, we now apply eq. (2) to calculate the future (2020-2028) and total (2007-2028) present discounted value (PDV) of operating profits. We assume that operating

profits in 2028 are the same as 2027. Table 12 presents the results for three discount rates, *r*=0.03, *r*=0.05 and *r*=0.07, using the low and high cost estimates. We estimate future operating profits between US$ 16,25 – 19,35 billion, and total operating profits of US$ 22,86 – 33,45 billion.

Table 12. Estimated PDV of operating profits between 2020-2028 and 2007-2028, applying eq. (2).

			In million 2018 US$	
	Discount rate (*r*)	**Estimation**	**2020-2028**	**2007-2028**
U.S.	**0.03**	**High**	9,308.62	21,257.71
		Low	9,261.67	21,161.71
	0.05	**High**	8,671.40	17,890.32
		Low	8,626.94	17,807.78
	0.07	**High**	8,108.78	15,294.15
		Low	8,066.53	15,222.02
Other HIC	**0.03**	**High**	1,979.46	4,871.73
		Low	1,946.13	4,799.74
	0.05	**High**	1,851.48	4,197.65
		Low	1,819.82	4,134.51
	0.07	**High**	1,738.05	3,674.54
		Low	1,707.89	3,618.27
MIC	**0.03**	**High**	2,155.00	3,167.92
		Low	2,080.49	3,072.18
	0.05	**High**	1,999.03	2,538.24
		Low	1,929.24	2,461.52
	0.07	**High**	1,861.39	2,064.21
		Low	1,795.75	2,001.83
GAVI	**0.03**	**High**	796.35	655.46
		Low	650.38	550.59
	0.05	**High**	742.64	484.96
		Low	605.26	407.37
	0.07	**High**	695.09	362.17
		Low	565.33	304.22
Indonesia/India	**0.03**	**High**	1,495.95	1,049.12
		Low	1,403.87	988.92
	0.05	**High**	1,380.28	755.72
		Low	1,294.83	712.36
	0.07	**High**	1,277.32	548.91
		Low	1,197.78	517.41
China	**0.03**	**High**	3,618.69	2,448.60
		Low	3,605.21	2,439.48
	0.05	**High**	3,252.32	1,707.46
		Low	3,240.20	1,701.10
	0.07	**High**	2,931.55	1,200.18
		Low	2,920.63	1,195.71
Total operating profits	**0.03**	**High**	19,354.08	33,450.55
		Low	18,947.75	33,012.61
	0.05	**High**	17,897.14	27,574.36
		Low	17,516.30	27,224.64
	0.07	**High**	16,612.17	23,144.17
		Low	16,253.91	22,859.46

Source: Own calculations based on Table 11 and assumption that 2028 values are the same as 2027.

5.3. Fixed Costs

Gardasil is currently manufactured in a dedicated facility built in Durham, North Carolina (Clendinen et al., 2016). Recently, Merck announced an expansion of the North Carolina facility and build a new one, the two facilities are expected to be fully operational from 2022 (Shamp, 2019). Since all factories are based in the U.S., we assume that the costs are the same in these additional factories and multiply the current fixed costs by three to obtain an estimate on total fixed costs from 2022 onwards.

Table 13a. Total fixed costs per year.

	Personnel	**Annual Salary (US$)**		**Total Costs (US$)**	
Number	**Type**	**Low**	**High**	**Low**	**High**
1	Director	150,000	200,000	150,000	200,000
3	Managers	100,000	150,000	300,000	450,000
7	Supervisors	70,000	100,000	490,000	700,000
Subtotal (in 2014 US$)				940,000.00	1,350,000.00
Subtotal (in 2018 US$)				1,000,000.00	1,436,170.21
Factory and administrative overhead (in 2018 US$)*				7,740,365.58	11,962,632.65
Total fixed costs per factory per year (in 2014 US$)				9,680,365.58	14,748,802.86
Total fixed costs per factory per year (in 2018 US$) (2007-2021)				**10,298,261.25**	**15,690,215.81**
Total fixed costs in 3 factories per year (from 2022)				**30,894,783.75**	**47,070,647.43**

* Derived in Table 13b.

Source: (Clendinen *et al.*, 2016) and own calculations.

Table 13b. Low and high estimate for the factory and administrative overhead.

		Low estimate (in 2018 US$)	**High estimate (in 2018 US$)**
Annual personnel cost	**Fixed***	1,000,000.00	1,436,170.21
	Variable (cost of 1 million x 28.55)*	6,952,110.39	9,732,954.55
Cost of materials (cost of 1 million x 28.55)*		9,248,702.01	15,414,503.35
Total		17,200,812.40	26,583,628.11
Factory and Administrative Overhead Costs (45% costs of personnel and material)		7,740,365.58	11,962,632.65

* Fixed labour costs are taken from Table 13a. ** For variable costs of labour and materials per one million doses, see Table 10. These are multiplied by the average number of doses sold per year between 2010-2017 (i.e. 28.55 million, according to Table 6a).

Source: Own calculations based on Table 11.

Table 13a lists the estimated annual fixed labour costs which correspond to salaries paid to the director, managers and supervisors for this factory. We also include "factory and administrative overhead" costs encompassing all the costs of maintenance of the facility and the equipment according to GMP guidelines (electricity, heating, cooling and operation of the machinery). As a convention

"factory and administrative overhead" correspond to 45% of the total cost for personnel and material (Clendinen et al., 2016). They are calculated in Table 13b

5.4. Estimated Global Value of Gardasil Patents and the Patent Buyout Price in 2020

Using eq. (3), Table 14 shows the present discounted value of the patent from 2007-2028 and 2020-2028 (median patent expiring year), based on the information in Table 12 and 13a on operating profits and fixed costs, respectively. The global patent buyout in 2020, considering the different real annual return to investment in alternative uses (*r*) and assuming patent expiry in 2028, vary between US$ 15,327.48 – 18,320.83 million (in 2018 US$). We did not include the operating profits for GAVI supported countries because these are not obliged to provide patent protection on vaccines until 2033 (MSF, 2017). We include those profits to derive the total patent value for 2007-2028 that we employ further in section 6. It amounts to US$ 22,294.26 – 33,079.75 million (in 2018 US$).

Table 14. Estimated global patent buyout in 2020 and total value of the Gardasil innovation, applying eq. (3).

		2020-2028 (in million 2018 US$)			2007-2028 (in million 2018 US$)		
Discount rate (*r*)	**Estimate**	**Operating profits***	**Fixed costs**	**Patent buyout price**	**Operating profits**	**Fixed costs**	**Patent value**
0.03	**High**	18,557.73	236.90	18,320.83	33,450.55	370.80	33,079.75
	Low	18,297.37	361.10	17,936.27	33,012.61	565.20	32,447.41
0.05	**High**	17,154.50	236.90	16,917.60	27,574.36	370.80	27,203.56
	Low	16,911.04	361.10	16,549.94	27,224.64	565.20	26,659.44
0.07	**High**	15,917.08	236.90	15,680.18	23,144.17	370.80	22,773.37
	Low	15,688.58	361.10	15,327.48	22,859.46	565.20	22,294.26

*We did not include operating profits from GAVI supported countries because these are not obliged to provide patent protection on vaccines until 2033.

Source: Own calculations based on Table 12 and Table 13a.

6. R&D Cost Estimates for Gardasil and Its Relation to the Patent Value

This section relates the total value of the Gardasil patents in Table 14 to its R&D costs. To calculate the R&D costs, we added the costs of clinical trials (phase I to III)[17]. We did not include the costs of pre-

[17] In phase I of clinical trials the vaccine is tested in a small number of healthy individual to identify the best route to administer the vaccine, frequency and dose escalation, the maximum tolerated dose (MTD) and side effects (Mahan, 2014). The main aim of phase II is to demonstrate the efficacy and immunogenicity of the vaccine

clinical development because it was mainly performed by academic institutions (Padmanabhan *et al.*, 2010).

To estimate the costs of each clinical trial we performed literature review coupled with a search in www.clinicaltrial.gov to identify the Gardasil related clinical trial sponsored by Merck. An earlier study estimated that the cost per subject (set-up, recruitment, administration and support) is between US$ 100-400 in phase I, US$ 300–400 in phase II and US$ 2000-3000 in phase III (inflation-adjusted costs in 2008 US$). We restate the information in Table 15 (Light *et al.*, 2009). To calculate how much was spent per clinical trial the number of subjects involved in the study was multiplied by the estimation of the cost per subject.

Table 15. Cost per subject per clinical trial phase

	Cost per subject (in 2008 US$)		Cost per subject (in 2018 US$)*	
	Low	**High**	**Low**	**High**
Phase I	100.00	400.00	116.28	465.12
Phase II	300.00	400.00	348.84	465.12
Phase III	2,000.00	3,000.00	2,325.58	3,488.37

* Deflated by PI from Table B.1.

Source: (Light *et al.*, 2009).

In addition to subject related costs, there are site (recruitment and retention of subjects, administrative and site monitoring) and study costs (data collection and management, institutional review board (IRB) approvals and amendments, source data verification, overheads and other costs). According to a previous study (Sertkaya *et al.*, 2016), the site costs are US$ 682,284 for phase I, US$ 3,791,310 for phase II and US$ 5,647,045 for phase III. The study costs for phase I is US$ 2,058,396, US$ 6,273,284 for phase II and US$9,063,763 for phase III. The data represent the mean costs from 2004-2012 and not adjusted for inflation. In Table 16, we thus used the PI from the median year (2008) to calculate the corresponding 2018 costs. Tables A.1 and A.2 in Appendix list the conducted studies for phases I to III testing Gardasil-4 and Gardasil-9, respectively. To calculate how much was spent on site and study costs per clinical trial phase, we multiply the number of studies on each phase by the estimated site and study costs of the corresponding phase.

candidate in a larger group (Mahan, 2014). In phase III the safety, immunogenicity and efficacy of the final dosage of the vaccine is tested in thousands of subjects and is tested against a placebo and/or another vaccine in the market (Lakdawalla, 2018).

Table 16. Site and study costs estimates for each phase of the clinical trial

	Phase I	Phase II	Phase III
Site costs			
Recruitment	51,904.00	233,729.00	395,182.00
Site retention	193,615.00	1,127,005.00	1,305,361.00
Administrative staff	237,869.00	1,347,390.00	2,321,628.00
Monitoring	198,896.00	1,083,186.00	1,624,874.00
Total (in 2008 US$)	**682,284.00**	**3,791,310.00**	**5,647,045.00**
Total (in 2018 US$)	**793,353.49**	**4,408,500.00**	**6,566,331.40**
Study costs			
Data management	50,331.00	59,934.00	39,047.00
IRB approvals	11,962.00	60,188.00	114,118.00
IRB amendments	1,094.00	1,698.00	1,919.00
Source data verification	326,437.00	406,038.00	400,173.00
Overheads	528,685.00	1,741,811.00	2,541,313.00
Other costs	1,139,887.00	4,003,615.00	5,967,193.00
Total (in 2008 US$)	**2,058,396.00**	**6,273,284.00**	**9,063,763.00**
Total (in 2018 US$)*	**2,393,483.72**	**7,294,516.28**	**10,539,259.30**

* Deflated by PI=0.86 for year 2008 from Table B.1.

Source: (Sertkaya *et al.*, 2016)

Using the information of Tables 15 and 16 jointly with the information on clinical trials in Table A.1, we estimate the R&D costs for all clinical phases for Gardasil-4 was between US$ 539,797,626 – 594,410,998, as shown in Table 17. Moreover, using Tables 15 and 16 jointly with the information on clinical trials in Table A.2, Table 17 displays the analogous R&D costs for Gardasil-9 in the range of US$ 419,175,907 – 458,228,307.

These R&D costs do not include capital costs that, unfortunately, are not available. We thus add a generous value of 15% to the costs estimated in Table 17 in order not to underestimate total R&D costs. As displayed in Table 18, the estimated total R&D costs of both vaccines is between US$ 1,102,822,520 – 1,210,547,032.

We now put our low and high estimate for total R&D costs in relation to the low and high estimate of the total innovation value, applying eq. (4). This provides us with a range for the theoretical innovation probability (μ) under free entry into R&D. The lower bound is found by dividing the low estimate for R&D costs from Table 18 (US$ 1,102.82 million) and the high estimate of the patent value (US$ 33,079.75 million) from Table 14, which gives us $\mu = 0.03$. For the upper bound, dividing the high estimate for R&D costs (US$ 1,210.54 million) and the low estimate of the patent value (US$ 22,294.26

million) implies $\mu = 0.05$. This suggests that the theoretical innovation probability is well below 10 percent – an astonishingly low figure.

Table 17. Estimated R&D costs on subjects, site and study of Gardasil-4 and Gardasil-9 (in 2018 US$)

		Estimate (in 2018 US$)			
		Gardasil-4		Gardasil-9	
		Low	High	Low	High
Phase-I	Total spent on subjects	94,069.77	376,279.07	18,372	73,488
	Total spent on sites	3,173,413.95	3,173,413.95	793,353.49	793,353.49
	Total spent of study costs	9,573,934.88	9,573,934.88	2,393,483.72	2,393,483.72
	Total spent on phase I clinical trials	12,841,418.60	13,123,627.91	3,202,637.21	3,250,037.21
Phase-II	Total spent on subjects	1,684,186.05	2,245,581.40	1,068,488.37	1,424,651.16
	Total spent on sites	22,042,500.00	22,042,500.00	17,634,000.00	17,634,000.00
	Total spent of study costs	36,472,581.40	36,472,581.40	29,178,065.12	29,178,065.12
	Total spent on phase II clinical trials	60,199,267.44	60,760,662.79	47,880,553.49	48,236,716.28
Phase-III	Total spent on subjects	107,539,534.88	161,309,302.33	77,297,674.42	115,946,511.63
	Total spent on sites	137,892,959.30	137,892,959.30	111,627,633.72	111,627,633.72
	Total spent of study costs	221,324,445.35	221,324,445.35	179,167,408.14	179,167,408.14
	Total spent on phase III clinical trials	466,756,939.53	520,526,706.98	368,092,716.28	406,741,553.49
	Total spent on clinical trials	539,797,625.58	594,410,997.67	419,178,479.07	458,238,595.35

Source: Own calculations based on Tables 15 and 16 jointly with Table A.1 for Gardasil-4 and Table A.2 for Gardasil-9.

Table 18. Total R&D cost derivation (in 2018 US$).

	Low estimate	High estimate
Gardasil-4 (subjects, site, study)	539,797,626	594,410,998
Gardasil-9 (subjects, site, study)	419,178,479	458,238,595
Subtotal (subjects, site, study)	**958,976,105**	**1,052,649,593**
Capital costs (15% of subtotal)	143,846,416	157,897,439
Total Gardasil R&D costs	**1,102,822,520**	**1,210,547,032**

Source: Own calculations based on Table 17.

7. Conclusion

Patent buyout is an effective strategy to lower vaccine prices, through allowing the entry of generic vaccines. We estimated that the remaining patent buyout value for Gardasil supplied by Merck in 2020 to be between US$ 15.33 – 18.32 billion (in 2018 US$), depending on the assumed discount rate to

value the future profit stream and some uncertainty regarding manufacturing costs. The estimated patent buyout price may be viewed as upper bound since the original manufacturer Merck would still be able to make profits after the patent buyout because of its brand name and its established production capacity.

Using information on clinical trials, we estimated the R&D costs for the Gardasil innovation to be around US$ 1.1 – 1.2 billion. Putting this into perspective to the total value of the Gardasil innovation, we arrive at a ratio of R&D costs to profits of the order of 3-5%.

Our methodology may be seen as fruitful for future research. We would need many more studies for all kinds of pharmaceuticals on patent buyout prices that potentially could serve to tackle public health problems especially of developing countries. Moreover, more information of the relationship between R&D costs and innovation values we could be useful to ask whether current patent protection laws may be more generous than needed to elicit desirable R&D effort, thus burdening health systems more than necessary.

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Appendix

Table A.1. Estimated costs of R&D from phase I to phase III clinical trial for Gardasil-4. All costs in 2018 US$.

Phase	#	Description	# of subjs	Costs estimation per subject (US$)		Calculated costs	
				Low	High	Low	High
Phase I	1**	• In one study subjects were given four dose formulations of HPV11 L1 VLP vaccine (10, 20, 50, and 100 ug). There were 28 subjects per dose level and 28 for the placebo group • In the other study three different formulations were used to test HPV16 L1 VLPs: 10 ug (13 active and four placebo), 40 ug (45 active and 15 placebo) and 80 ug (24 active and eight placebo). • Source: (Fife *et al.*, 2004)	249	116	465	28,953	115,814
	2**	• Forty women, aged 16-23 years, were randomly assigned (2:1 vaccine to placebo ratio) to receive either HPV18 L1 VLP vaccine or placebo. •Source: (Ault *et al.*, 2004)	40	116	465	4,651	18,605
	3**	• Healthy nonpregnant women aged 18 to 26 years old were assigned to study groups to receive placebo or a 3-dose regime of the different HPV 16 L1 VLP vaccine dosage of 10 µg (n=112), 20 µg (n=105), 40 µg (n=104), or 80 µg (n=107). • Source: (Poland *et al.*, 2005)	480	116	465	55,814	223,256
	4	• Females aged 9-26 year were vaccinated with a single dose of Gardasil in an open label study to evaluate safety and tolerability of the vaccine. • From: March 2008-April 2008 • ID: NCT00635830	40	116	465	4,651	18,605
	Total spent on subjects on phase I					94,070	376,279
	Total spent on sites (number of studies x 793,353.49*)					3,173,414	3,173,414
	Total spent of study costs (number of studies x 2,393,483.72*)					9,573,935	9,573,935
	Total spent on phase I clinical trials					12,841,419	13,123,628
Phase II	1	• Young women aged 16-23 years old were randomly assigned to receive three doses of placebo (n=1198) or HPV-16 virus-like–particle vaccine (n=1194) • From: September 1999- March 2004 • ID: NCT00365378	2,392	349	465	834,419	1,112,558
	2	• A total of 831 women aged 16-23 years were vaccinated with one of the three formulations quadrivalent HPV (Types 6/11/16/18) L1 virus-like particle (VLP) (each of the 3 groups had 275-280 subjects) or received one of the two placebo formulations (n=275). Dose escalation assessment (n=52). • From: May 2000-May 2004 • ID: NCT00365716	1,158	349	465	403,953	538,605

	3	• Women aged 18-26 years were assigned to receive Gardasil vaccination (n=509) or placebo (n=512) • From: June 2006-September 2009 • ID: NCT00378560	1,021	349	465	356,163	474,884
	4	• Evaluate the effectiveness of Gardasil in men aged 27-45 who have completed 4 years of observation in HPV infection in men • Duration: December 2012 - October 2019 • ID: NCT01432574	150	349	465	52,326	69,767
	5	• The immunogenicity, safety and tolerability of the quadrivalent vaccine was assessed in females Aged 9-17 years. • From: December 2006 - September 2009 • ID: NCT00411749	107	349	465	37,326	49,767
	Total spent on subjects on phase II					**1,684,186**	**2,245,581**
	Total spent on sites (number of studies x 4,408,500.00*)					22,042,500	22,042,500
	Total spent of study costs (number of studies x 7,294,516.28*)					36,472,581	36,472,581
	Total spent on phase II clinical trials					**60,199,267**	**60,760,663**
Phase III	1	• Women aged 16-24 year were randomly assigned to receive 3 doses of the quadrivalent vaccine (2723) or placebo (n=2732). • From: December 2001-January 2009; ID: NCT00092521	5,455	2,326	3,488	12,686,047	19,029,070
	2	• Women aged 16-23 were randomized (1:1:1:1) to receive three doses of quadrivalent HPV-6/11/16/18 vaccine co-administered with HBV vaccine, quadrivalent vaccine with HBV-vaccine matched placebo, HBV vaccine with HPV-vaccine matched placebo, or HPV-vaccine matched placebo and HBV-vaccine matched placebo. • From: December 2001 - June 2004 • ID: NCT00517309	1,871	2,326	3,488	4,351,163	6,526,744
	3	• Women aged 16-23 years in a phase III study to compare the immunogenicity and safety of the quadrivalent Gardasil and Monovalent HPV 16 vaccine. • From: June 2002 - June 2004 • ID: NCT00092482	3,882	2,326	3,488	9,027,907	13,541,860
	4	• Women aged 15-26 were randomly assigned 1:1 to receive 3 doses of the quadrivalent vaccine or placebo • From: June 2002 - July 2007 • ID: NCT00092534	12,167	2,326	3,488	28,295,349	42,443,023
	5	• Women age 10-23 years were randomly assigned to receive placebo or Gardasil to assess the immune response to the 4 components of the vaccine. • From: December 2002 - September 2004 • ID: NCT00092495	3,055	2,326	3,488	7,104,651	10,656,977

6	• Adolescents aged 9 to 15 years were randomly assigned 2:1 to receive HPV4 vaccine or saline placebo. On the 30th, the placebo group (n = 482) received the same regimen of HPV4 vaccine and both cohorts were followed through month 96. • From: October 2003 - November 2005 • ID: NCT00092547	1,781	2,326	3,488	4,141,860	6,212,791
7	• Women aged 24-45 years were receive 3 doses of Gardasil (n=1911) or placebo (1908). • ID: NCT00090220 • From: June 2004 - May 2009	3,819	2,326	3,488	8,881,395	13,322,093
8	• Heterosexual males aged 16-24 (n=3463) and homosexual men aged 16–24 years (n= 602) were randomly assigned to receive three doses of Gardasil (n=2032) or placebo (n=2033). • From: September 2004 - July 2009 • ID: NCT00090285	4,065	2,326	3,488	9,453,488	14,180,233
9	• Females aged 9–23 years were randomly assigned to receive three doses of Gardasil (n=117) or placebo (n=59). • From: October 2005 - June 2006 • ID : NCT00157950	176	2,326	3,488	409,302	613,953
10	• Adolescents (394 boys and 648 girls) aged 10-17 years were randomly assigned in a 1:1 ratio to receive: 3 doses of Gardasil with one dose of Menactra and Adacel (concomitant), 3 of Gardasil with one dose of Menactra and Adacel (nonconcomitant). • From: April 2006 - April 2007 • ID: NCT00325130	1,042	2,326	3,488	2,423,256	3,634,884
11	• Teenage boys and girls aged 11-17 were enrolled in an open-label study in which all subjects received three doses of GARDASIL and one of REPEVAX. • From: May 2006-May 2007 • ID: NCT00337428	843	2,326	3,488	1,960,465	2,940,698
12	• Women aged 9-15 years participated in the study to evaluate the safety and tolerability of Gardasil. • From: May 2007-February 2008 • ID: NCT00380367	110	2,326	3,488	255,814	383,721
13	• Chinese females aged 9-45 years (n=500) and males aged 9 to 15 years (n=100) were randomly assigned in a 1:1 ratio to receive either 3 doses of Gardasil or aluminum-containing placebo. • From: July 20, 2008-February 28, 2009 • ID: NCT00496626	600	2,326	3,488	1,395,349	2,093,023
14	• Females aged 20-45 years were assigned to receive three doses of Gardasil or placebo to test the safety and effectiveness of the vaccine. • From: December 31, 2008- May 11, 2012 • ID: NCT00834106	3,006	2,326	3,488	6,990,698	10,486,047

15	• Sub-Saharan females aged 9-26 were enrolled in the study to evaluate safety, tolerability and immunogenicity of the three dose Gardasil. Thirty females ages 13-15 and 120 females ages 16-26 received the three dose Gardasil. In addition, girls aged 9-12 years were randomized in a 4:1 ratio to receive either Gardasil (n = 80) or placebo (n = 20). • From: March 2011 - April 2013 • ID: NCT01245764	250	2,326	3,488	581,395	872,093
16	• Open label study to evaluate Gardasil`s safety and effectiveness in females aged 16- to 26 years. • From: November 2011-August 2016 • ID: NCT01544478	1,030	2,326	3,488	2,395,349	3,593,023
17	• Japanese males aged 16-26 year were enrolled in a study to evaluate the efficacy and tolerability of Gardasil. • From: June 2013 - August 2017 • ID: NCT01862874	1,124	2,326	3,488	2,613,953	3,920,930
18	• Evaluate the immunogenicity, safety, and tolerability of Gardasil in females aged 9-26 years • Duration: August 2018 - October 2023 • ID: NCT03493542	766	2,326	3,488	1,781,395	2,672,093
19	• Evaluate Two-dose schedule of Gardasil-4 in 11-year-old Boys • Duration: February 2015 - December 2015 • ID: NCT02382900	500	2,326	3,488	1,162,791	1,744,186
20	• Evaluate tolerability and immunogenicity of a 3-dose regimen of Gardasil administered to healthy married females aged 16-23 years • Duration: October 2009 - October 2013 • ID: NCT00733122	600	2,326	3,488	1,395,349	2,093,023
21	• Boys aged 9-15 years were enrolled in an open label two-part study in which part 1 assessed immunogenicity and tolerability of Gardasil up to Month 7 whereas part 2 assessed long-term immunogenicity and safety (Month 7-Month 30). • From: November 2015 - August 2018 • ID: NCT02576054	100	2,326	3,488	232,558	348,837
Total spent on subjects on phase III					**107,539,535**	**161,309,302**
Total spent on sites (number of studies x 6,566,331.40*)					137,892,959	137,892,959
Total spent of study costs (number of studies x 10,539,259.30*)					221,324,445	221,324,445
Total spent on phase III clinical trials					**466,756,940**	**520,526,707**
Total cost of all phases					**539,797,626**	**594,410,998**

* From estimates displayed in Table 16.

** Clinical trial was not registered on www.clinicaltrial.gov thus they do not have an ID. However, results were published in peer reviewed journals cited in the description (source).

Table A.2. Estimated costs of R&D from phase I to phase III clinical trial for Gardasil-9. All costs in 2018 US$.

Phase	#	Description	# of subjs	Costs estimation per subject (US$)		Calculated costs	
				Low	High	Low	High
Phase I	1	• Evaluate the safety and tolerability of octavalent HPV L1 VLP vaccine formulated with amorphous aluminum hydroxysulfate and ISCOMATRIX in females aged 18-24 years • Duration: April 2006 - November 2009 • ID: NCT00851643	158	116	465	18,372	73,488
	Total spent on subjects on phase I					18,372	73,488
	Total spent on sites (number of studies x 793,353.49*)					793,353	793,353
	Total spent of study costs (number of studies x 2,393,483.72*)					2,393,484	2,393,484
	Total spent on phase I clinical trials					**3,202,637**	**3,250,037**
Phase II	1	• Determine immunogenicity, safety and tolerability of Gardasil-4 and 9 vaccine in young cancer survivors aged 9-26 years • Duration: July 2012 - November 2020 • ID: NCT01492582	1252	349	465	436,744	582,326
	2	• Females aged 16-23 years were enrolled in a study to evaluate the tolerability and immunogenicity of the 3-dose vaccine. • From: December 2005 - August 2007 • ID: NCT00260039	680	349	465	237,209	316,279
	3	• Compare safety and immunogenicity of V505 HPV vaccine candidate and Gardasil-4 in females 16-26 years • Duration: October 2007-May 2011 • ID: NCT00520598	511	349	465	178,256	237,674
	4	• Examine tolerability and immunogenicity HPV L1 VLP vaccine candidate administered Concomitantly with Gardasil in females aged 16-26. • Duration: October 2007 - May 2009 • ID: NCT00551187	620	349	465	216,279	288,372
	Total spent on subjects on phase II					1,068,488	1,424,651
	Total spent on sites (number of studies x 4,408,500.00*)					17,634,000	17,634,000
	Total spent of study costs (number of studies x 7,294,516.28*)					29,178,065	29,178,065
	Total spent on phase II clinical trials					47,880,553	48,236,716
Phase III	1	• A Phase III Open-label Safety and Immunogenicity Study of GARDASIL™9 Administered to 9- to 26-Year-Old Females and Males in Vietnam • Duration: June 2018 - January 2019 • ID: NCT03546842	200	2,326	3,488	465,116	697,674
	2	• This study will assess the safety and immunogenicity of GARDASIL®9 (V503) in 27- to 45-year-old women	1212	2,326	3,488	2,818,605	4,227,907

		• Duration: September 2017 - November 2018 • ID: NCT03158220					
	3	• Examine the acceptability, uptake and immunogenicity of the vaccine in the postpartum setting in women 16 years to 26 years • Duration: November 2018 - July 2019 • ID: NCT03451071	200	2,326	3,488	465,116	697,674
	4	• Assess occupational exposure to Human Papilloma Virus (HPV) and prophylactic vaccination in healthcare workers aged 27-69 • Country: USA • Duration: February 2018 - November 2018 • ID: NCT03350698	100	2,326	3,488	232,558	348,837
	5	• Evaluate the Immunogenicity of the nonvalent vaccine against Human Papillomavirus in men (age 18-36 years) infected by HIV who have sex with men. • Duration: October 2018 - December 2021 • ID: NCT03626467	166	2,326	3,488	386,047	579,070
	6	• Assess the efficacy of HPV vaccine in reducing high-grade cervical lesions in patients with HPV and HIV infections in females aged 25 and older • Duration: January 2019 - October 2021 • ID: NCT03284866	536	2,326	3,488	1,246,512	1,869,767
	7	• Assess the safety and immunogenicity of a 2-dose regimen of Gardasil-9 (V503) in boys and girls 9 to 14 years of age and in young women aged 16-26 years • Duration: November 2013 - August 2018 • ID: NCT01984697	1518	2,326	3,488	3,530,233	5,295,349
	8	• Assess safety, immunogenicity and long-term effectiveness Gardasil-9 in preventing cervical cancer and related precancers caused by HPV types covered in the vaccine in females aged 16-26 years • Duration: January 2016 - January 2024 • ID: NCT02653118	4453	2,326	3,488	10,355,814	15,533,721
	9	• Evaluate immunogenicity and tolerability of Gardasil-9 administered Concomitantly with Menactra and Adacel in boys and girls aged 11-15 year • Duration: October 2009 - February 2011 • ID: NCT00988884	1241	2,326	3,488	2,886,047	4,329,070
	10	• Evaluate tolerability of Gardasil-9 in females aged 12-26 years who were previously vaccinated with GARDASIL-4 • Duration: February 2010 - November 2015 • ID: NCT01047345	924	2,326	3,488	2,148,837	3,223,256

11	• Evaluate if Gardasil-9 induces non-inferior Geometric Mean Titres (GMTs) for serum anti-HPV 6, 11, 16, and 18, compared to GARDASIL-4 in males aged 16 – 26 year • Duration: March 2014 - April 2015 • ID: NCT02114385	500	2,326	3,488	1,162,791	1,744,186
12	• Compare immunogenicity and tolerability of Gardasil-4 and 9 in females ages 9-15 years • Duration: February 2011 - December 2011 • ID: NCT01304498	600	2,326	3,488	1,395,349	2,093,023
13	• Evaluate whether if first dose of Gardasil-9 concomitantly administrated with REPEVAX™ is well tolerated and equally immunogenic compared to administration of REPEVAX a month after Gardasil-9 first dose • Countries: Finland, Germany, Denmark, Thailand, Belgium, Austria • Duration: April 2010 - June 2011 • ID: NCT01073293	1054	2,326	3,488	2,451,163	3,676,744
14	• Evaluate safety, tolerability and Immunogenicity of Gardasil-9 in Japanese girls aged 9-15 year • Duration: January 2011 - August 2013 • ID: NCT01254643	100	2,326	3,488	232,558	348,837
15	• Assess immunogenicity and tolerability of Gardasil-9 in males and females aged 9-15 years • Duration: August 2009 - December 2020 • ID: NCT00943722	3074	2,326	3,488	7,148,837	10,723,256
16	• Compare the safety, efficacy, and immunogenicity of Gardasil-4 and 9 in females aged 16-26 years old. • Duration: September 2007 - July 2016 • ID: NCT00543543	14840	2,326	3,488	34,511,628	51,767,442
17	• Evaluate immunogenicity and tolerability of Gardasil-9 in males and females aged 16-26 years • Duration: October 2012 - August 2014 • ID: NCT01651949	2520	2,326	3,488	5,860,465	8,790,698
Total spent on subjects on phase III					**77,297,674**	**115,946,512**
Total spent on sites (number of studies x 6,566,331.40*)					111,627,634	111,627,634
Total spent of study costs (number of studies x 10,539,259.30*)					179,167,408	179,167,408
Total spent on phase III clinical trials					**368,092,716**	**406,741,553**
Total costs of all phases					**419,178,479.07**	**458,238,595.35**

* From estimates displayed in Table 16.

References

Ault, K. A., Giuliano, A. R., Edwards, R. P., Tamms, G., Kim, L.-L., Smith, J. F., Jansen, K. U., Allende, M., Taddeo, F. J., Skulsky, D. and Barr, E. (2004) 'A phase I study to evaluate a human papillomavirus (HPV) type 18 L1 VLP vaccine', *Vaccine*. Elsevier, 22(23–24), pp. 3004–3007. doi: 10.1016/J.VACCINE.2004.02.020.

Bosch, F. X., Burchell, A. N., Schiffman, M., Giuliano, A. R., de Sanjose, S., Bruni, L., Tortolero-Luna, G., Kjaer, S. K. and Muñoz, N. (2008) 'Epidemiology and Natural History of Human Papillomavirus Infections and Type-Specific Implications in Cervical Neoplasia', *Vaccine*, 26, pp. K1–K16. doi: 10.1016/j.vaccine.2008.05.064.

Castro, A., Cinà, M., Helmer-Smith, M., Vlček, C., Oghor, C. and Cazabon, D. (2017) 'A case study of Gavi'S human papillomavirus vaccine support programme', *Journal of Health Specialties*. Medknow Publications and Media Pvt. Ltd., 5(1), p. 2. doi: 10.4103/2468-6360.198797.

CDC (2018a) *Archived CDC Vaccine Price Lists*, *US Centers for Disease Control and Prevention*. Available at: https://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/archive.html (Accessed: 11 October 2018).

CDC (2018b) *Vaccines and Immunizations*, *Center for Disease Control and Prevention*. Available at: https://www.cdc.gov/vaccines/index.html (Accessed: 11 October 2018).

Chandrasekharan, S., Amin, T., Kim, J., Furrer, E., Matterson, A.-C., Schwalbe, N. and Nguyen, A. (2015) 'Intellectual property rights and challenges for development of affordable human papillomavirus, rotavirus and pneumococcal vaccines: Patent landscaping and perspectives of developing country vaccine manufacturers', *Vaccine*. Elsevier, 33(46), pp. 6366–6370. doi: 10.1016/J.VACCINE.2015.08.063.

Chesson, H. W., Ekwueme, D. U., Saraiya, M., Watson, M., Lowy, D. R. and Markowitz, L. E. (2012) 'Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States', *Vaccine*. Elsevier, 30(42), pp. 6016–6019. doi: 10.1016/J.VACCINE.2012.07.056.

Cheung, E. and Zhang, K. (2018) 'Hong Kong medical centres under fire after selling HPV cervical cancer vaccine Gardasil 9 when they couldn't get it', *South China Morning Post*. Available at: https://www.scmp.com/news/hong-kong/health-environment/article/2151174/hong-kong-medical-centres-under-fire-after-selling.

Choi, Y. H., Chapman, R., Gay, N. and Jit, M. (2012) 'Potential overestimation of HPV vaccine impact due to unmasking of non-vaccine types: Quantification using a multi-type mathematical model',

Vaccine. Elsevier, 30(23), pp. 3383–3388. doi: 10.1016/J.VACCINE.2012.03.065.

Clendinen, C., Zhang, Y., Warburton, R. N. and Light, D. W. (2016) 'Manufacturing costs of HPV vaccines for developing countries.', *Vaccine*, 34(48), pp. 5984–5989. doi: 10.1016/j.vaccine.2016.09.042.

Clifford, G., Gallus, S., Herrero, R., *et al.* (2005) 'Worldwide distribution of human papillomavirus types in cytologically normal women in the International Agency for Research on Cancer HPV prevalence surveys: a pooled analysis', *The Lancet*. Elsevier, 366(9490), pp. 991–998. doi: 10.1016/S0140-6736(05)67069-9.

Das, M. (2018) 'Cervical cancer vaccine controversy in India.', *The Lancet. Oncology*. Elsevier, 19(2), p. e84. doi: 10.1016/S1470-2045(18)30018-4.

Diaz-Padilla, I., Monk, B. J., Mackay, H. J. and Oaknin, A. (2013) 'Treatment of metastatic cervical cancer: Future directions involving targeted agents', *Critical Reviews in Oncology/Hematology*, 85(3), pp. 303–314. doi: 10.1016/j.critrevonc.2012.07.006.

EMA (2009) *Gardasil*, *European Medical Agency*. Available at: https://www.ema.europa.eu/en/medicines/human/EPAR/gardasil (Accessed: 25 May 2019).

Federal Reserve Bank (2018) *Consumer Price Index: All Items for the United States*, *FRED Economic Data*. Available at: https://fred.stlouisfed.org/series/USACPIALLAINMEI (Accessed: 21 June 2019).

Fife, K. H., Wheeler, C. M., Koutsky, L. A., *et al.* (2004) 'Dose-ranging studies of the safety and immunogenicity of human papillomavirus Type 11 and Type 16 virus-like particle candidate vaccines in young healthy women', *Vaccine*. Elsevier, 22(21–22), pp. 2943–2952. doi: 10.1016/J.VACCINE.2003.11.058.

Frisch, M. and Goodman, M. T. (2000) 'Human papillomavirus-associated carcinomas in Hawaii and the mainland U.S.', *Cancer*, 88(6), pp. 1464–9. Available at: http://www.ncbi.nlm.nih.gov/pubmed/10717631 (Accessed: 15 November 2018).

Galasso, A., Mitchell, M. and Virag, G. (2016) 'Market outcomes and dynamic patent buyouts', *International Journal of Industrial Organization*. North-Holland, 48, pp. 207–243. doi: 10.1016/J.IJINDORG.2016.06.007.

Garland, S. M., Hernandez-Avila, M., Wheeler, C. M., *et al.* (2007) 'Quadrivalent Vaccine against Human Papillomavirus to Prevent Anogenital Diseases', *New England Journal of Medicine*. Massachusetts Medical Society , 356(19), pp. 1928–1943. doi: 10.1056/NEJMoa061760.

GAVI (2017) *Supply and Procurement Roadmap - Human Papilloma Virus Vaccine*. Geneva. Available

at: https://www.gavi.org/about/market-shaping/supply-and-procurement-roadmaps/.

GAVI (2018) *About Gavi, the Vaccine Alliance*, *GAVI*. Available at: https://www.gavi.org/about/ (Accessed: 25 September 2018).

Gertig, D. M., Brotherton, J. M., Budd, A. C., Drennan, K., Chappell, G. and Saville, A. M. (2013) 'Impact of a population-based HPV vaccination program on cervical abnormalities: a data linkage study', *BMC Medicine*, 11(1), p. 227. doi: 10.1186/1741-7015-11-227.

Giuliano, A. R., Palefsky, J. M., Goldstone, S., *et al.* (2011) 'Efficacy of Quadrivalent HPV Vaccine against HPV Infection and Disease in Males', *New England Journal of Medicine*, 364(5), pp. 401–411. doi: 10.1056/NEJMoa0909537.

Goldie, S. J., O'Shea, M., Campos, N. G., Diaz, M., Sweet, S. and Kim, S.-Y. (2008) 'Health and economic outcomes of HPV 16,18 vaccination in 72 GAVI-eligible countries', *Vaccine*, 26(32), pp. 4080–4093. doi: 10.1016/j.vaccine.2008.04.053.

Grimaldi-Bensouda, L., Guillemot, D., Godeau, B., *et al.* (2014) 'Autoimmune disorders and quadrivalent human papillomavirus vaccination of young female subjects', *Journal of Internal Medicine*, 275(4), pp. 398–408. doi: 10.1111/joim.12155.

GSK (2008) *GSK Annual Report 2007*. Available at: http://www.annualreports.com/Company/glaxosmithkline-plc.

GSK (2011) *GSK Annual Report 2010*. Available at: http://www.annualreports.com/Company/glaxosmithkline-plc.

GSK (2014) *GSK Annual Report 2013*. Available at: http://www.annualreports.com/Company/glaxosmithkline-plc.

GSK (2017) *GSK Annual Report 2016*. Available at: http://www.annualreports.com/Company/glaxosmithkline-plc.

GSK (2018) *Annual report 2017*. London. Available at: https://www.gsk.com/en-gb/investors/corporate-reporting/annual-report-2017/.

Health Canada (2018) *Patent Register - Drug Products*, *Government of Canada*. Available at: http://pr-rdb.hc-sc.gc.ca/pr-rdb/patent_result-resultat_brevet.do?action=search_recherche&din=02437058&patentNumber_numeroBrevet=2479304&drugId=4404&lang=fr&formId=8816 (Accessed: 17 December 2018).

Hongyu, B. (2018) 'HPV vaccines to become more readily available in China', *People's Daily Online*. Available at: http://en.people.cn/n3/2018/0531/c90000-9466329.html.

Insinga, R. P., Dasbach, E. J. and Elbasha, E. H. (2005) 'Assessing the Annual Economic Burden of Preventing and Treating Anogenital Human Papillomavirus-Related Disease in the US', *PharmacoEconomics*. Springer International Publishing, 23(11), pp. 1107–1122. doi: 10.2165/00019053-200523110-00004.

Kosen, S., Andrijono, A., Ocviyanti, D. and Indriatmi, W. (2017) 'The Cost-Effectiveness of Quadrivalent Human Papillomavirus Vaccination in Indonesia', *Asian Pacific journal of cancer prevention : APJCP*. Shahid Beheshti University of Medical Sciences, 18(7), pp. 2011–2017. doi: 10.22034/APJCP.2017.18.7.2011.

Kremer, M. (1998) 'Patent Buyouts: A Mechanism for Encouraging Innovation', *The Quarterly Journal of Economics*. Oxford University Press, 113(4), pp. 1137–1167. doi: 10.1162/003355398555865.

Lakdawalla, D. N. (2018) 'Economics of the Pharmaceutical Industry', *Journal of Economic Literature*, 56(2), pp. 397–449. Available at: http://www.aeaweb.org/articles?id=10.1257/jel.20161327.

Lebelo, R. L., Boulet, G., Nkosi, C. M., Bida, M. N., Bogers, J.-P. and Mphahlele, M. J. (2014) 'Diversity of HPV types in cancerous and pre-cancerous penile lesions of South African men: Implications for future HPV vaccination strategies', *Journal of Medical Virology*, 86(2), pp. 257–265. doi: 10.1002/jmv.23730.

Light, D. W., Andrus, J. K. and Warburton, R. N. (2009) 'Estimated research and development costs of rotavirus vaccines', *Vaccine*. Elsevier, 27(47), pp. 6627–6633. doi: 10.1016/J.VACCINE.2009.07.077.

Louie, K. S., De Sanjose, S. and Mayaud, P. (2009) 'Epidemiology and prevention of human papillomavirus and cervical cancer in sub-Saharan Africa: a comprehensive review', *Tropical Medicine & International Health*. Wiley/Blackwell (10.1111), 14(10), pp. 1287–1302. doi: 10.1111/j.1365-3156.2009.02372.x.

Luna, J., Plata, M., Gonzalez, M., Correa, A., Maldonado, I., Nossa, C., Radley, D., Vuocolo, S., Haupt, R. M. and Saah, A. (2013) 'Long-Term Follow-up Observation of the Safety, Immunogenicity, and Effectiveness of Gardasil™ in Adult Women', *PLoS ONE*. Edited by S. Pett, 8(12), p. e83431. doi: 10.1371/journal.pone.0083431.

Ma, B., Roden, R. and Wu, T.-C. (2010) 'Current status of human papillomavirus vaccines.', *Journal of the Formosan Medical Association = Taiwan yi zhi*. NIH Public Access, 109(7), pp. 481–3. Available at: http://www.ncbi.nlm.nih.gov/pubmed/20677402 (Accessed: 9 November 2018).

Macartney, K., Chiu, C., Safety, M. G.-D. and 2013, undefined (no date) 'Safety of human papillomavirus vaccines: a review', *Springer*. Available at: https://idp.springer.com/authorize/casa?redirect_uri=https://link.springer.com/article/10.1007/s40

264-013-0039-5&casa_token=N4UoLRhhM8EAAAAA:1isXsSNozYlpdGjaWRPLaR3yU3wWaZVwdhMFvIjLSeMt2JvxMqFD3dZ7U2gMAFlznB_OPgxom7AkROOx (Accessed: 15 November 2018).

MacroTrends (2019) *Pound Dollar Exchange Rate (GBP USD) - Historical Chart*, *MacroTrends*. Available at: https://www.macrotrends.net/2549/pound-dollar-exchange-rate-historical-chart (Accessed: 13 October 2019).

Mahan, V. L. (2014) 'Clinical Trial Phases', *International Journal of Clinical Medicine*, 5, pp. 1374–1383. doi: 10.4236/ijcm.2014.521175.

Mahoney, R. T. (1990) 'Cost of plasma-derived hepatitis B vaccine production', *Vaccine*. Elsevier, 8(4), pp. 397–401. doi: 10.1016/0264-410X(90)90101-Q.

Mahoney, R. T., Francis, D. P., Frazatti-Gallina, N. M., Precioso, A. R., Raw, I., Watler, P., Whitehead, P. and Whitehead, S. S. (2012) 'Cost of production of live attenuated dengue vaccines: A case study of the Instituto Butantan, Sao Paulo, Brazil', *Vaccine*. Elsevier, 30(32), pp. 4892–4896. doi: 10.1016/J.VACCINE.2012.02.064.

McGraw, S. L. and Ferrante, J. M. (2014) 'Update on prevention and screening of cervical cancer.', *World journal of clinical oncology*. Baishideng Publishing Group Inc, 5(4), pp. 744–52. doi: 10.5306/wjco.v5.i4.744.

McKee, S. J., Bergot, A.-S. and Leggatt, G. R. (2015) 'Recent progress in vaccination against human papillomavirus-mediated cervical cancer', *Reviews in Medical Virology*. Wiley-Blackwell, 25, pp. 54–71. doi: 10.1002/rmv.1824.

Merck (2008) *Merck & Co. 2007 annual report as filed with the Securities and Exchange Commission*. Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Merck (2009) *Merck & Co. 2008 annual report as filed with the Securities and Exchange Commission*. Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Merck (2012) *Merck & Co., Inc. 2011 annual report as filed with the Securities and Exchange Commission*. Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Merck (2015) *Merck & Co., Inc. 2014 annual report as filed with the Securities and Exchange Commission*. Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Merck (2017) *Merck & Co. 2016 annual report as filed with the Securities and Exchange Commission*.

Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Merck (2018) *Merck & Co., Inc. 2017 annual report as filed with the Securities and Exchange Commission*. Washington, D.C. Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Merck (2019) *Merck & Co., Inc. 2018 annual report as filed with the Securities and Exchange Commission*. Available at: https://investors.merck.com/financials/annual-reports-and-proxy/default.aspx.

Moreira, E. D., Palefsky, J. M., Giuliano, A. R., *et al.* (2011) 'Safety and reactogenicity of a quadrivalent human papillomavirus (types 6, 11, 16, 18) L1 viral-like-particle vaccine in older adolescents and young adults', *Human Vaccines*, 7(7), pp. 768–775. doi: 10.4161/hv.7.7.15579.

Morgan, S., Grootendorst, P., Lexchin, J., Cunningham, C. and Greyson, D. (2011) 'The cost of drug development: A systematic review', *Health Policy*. Elsevier, 100(1), pp. 4–17. doi: 10.1016/J.HEALTHPOL.2010.12.002.

MSF (2017) *A Fair Shot for Vaccine Affordability*. Geneva. Available at: https://msfaccess.org/sites/default/files/2018-06/VAC_report_A Fair Shot for Vaccine Affordability_ENG_2017.pdf (Accessed: 17 December 2018).

Mueller-Langer, F. (2013) 'Neglected infectious diseases: Are push and pull incentive mechanisms suitable for promoting drug development research?', *Health Economics, Policy and Law*. Cambridge University Press, 8(02), pp. 185–208. doi: 10.1017/S1744133112000321.

Nguyen, A., Datta, D., Schwalbe, N., Summers, D. and Adlide, G. (2011) 'Working towards affordable pricing for HPV vaccines for developing countries: The role of GAVI', *Harvard Global Equity Initiative*.

Ooms, G., Forman, L., Williams, O. D. and Hill, P. S. (2014) 'Could international compulsory licensing reconcile tiered pricing of pharmaceuticals with the right to health?', *BMC International Health and Human Rights*. BioMed Central, 14(1), p. 37. doi: 10.1186/s12914-014-0037-4.

Outterson, K. (2005) 'Pharmaceutical arbitrage: balancing access and innovation in international prescription drug markets.', *Yale journal of health policy, law, and ethics*, 5(1), pp. 193–291. Available at: http://www.ncbi.nlm.nih.gov/pubmed/15742578 (Accessed: 14 November 2018).

Padmanabhan, S., Amin, T., Sampat, B., Cook-Deegan, R. and Chandrasekharan, S. (2010) 'Intellectual property, technology transfer and manufacture of low-cost HPV vaccines in India', *Nature Biotechnology*, 28(7), pp. 671–678. doi: 10.1038/nbt0710-671.

PAHO (2019) *PAHO Revolving Fund*, *PAHO*. Available at:

https://www.paho.org/hq/index.php?option=com_content&view=category&view=article&id=1864&Itemid=2234&lang=en (Accessed: 28 January 2019).

Poland, G. A., Jacobson, R. M., Koutsky, L. A., Tamms, G. M., Railkar, R., Smith, J. F., Bryan, J. T., Cavanaugh, P. F., Jansen, K. U. and Barr, E. (2005) 'Immunogenicity and Reactogenicity of a Novel Vaccine for Human Papillomavirus 16: A 2-Year Randomized Controlled Clinical Trial', *Mayo Clinic Proceedings*. Elsevier, 80(5), pp. 601–610. doi: 10.4065/80.5.601.

Qazi, S., Aboubaker, S., MacLean, R., Fontaine, O., Mantel, C., Goodman, T., Young, M., Henderson, P. and Cherian, T. (2015) 'Ending preventable child deaths from pneumonia and diarrhoea by 2025. Development of the integrated Global Action Plan for the Prevention and Control of Pneumonia and Diarrhoea.', *Archives of disease in childhood*. BMJ Publishing Group Ltd, 100 Suppl 1(Suppl 1), pp. S23-8. doi: 10.1136/archdischild-2013-305429.

Sabeena, S., Bhat, P. V., Kamath, V. and Arunkumar, G. (2018) 'Global human papilloma virus vaccine implementation: An update', *Journal of Obstetrics and Gynaecology Research*. John Wiley & Sons, Ltd (10.1111), 44(6), pp. 989–997. doi: 10.1111/jog.13634.

Sagonowsky, E. (2018) 'Boosted by China launch, Merck's Gardasil turns in a big first-quarter performance', *FiercePharma*. Available at: https://www.fiercepharma.com/pharma/boosted-by-china-launch-merck-s-gardasil-turns-a-big-first-quarter-performance.

Sandø, N., Kofoed, K., Zachariae, C. and Fouchard, J. (2014) 'A Reduced National Incidence of Anogenital Warts in Young Danish Men and Women after Introduction of a National Quadrivalent Human Papillomavirus Vaccination Programme for Young Women – An Ecological Study', *Acta Dermato Venereologica*, 94(3), pp. 288–292. doi: 10.2340/00015555-1721.

Saxena, U., Sauvaget, C. and Sankaranarayanan, R. (2012) 'Evidence-based screening, early diagnosis and treatment strategy of cervical cancer for national policy in low- resource countries: example of India.', *Asian Pacific journal of cancer prevention : APJCP*, 13(4), pp. 1699–703. Available at: http://www.ncbi.nlm.nih.gov/pubmed/22799391 (Accessed: 15 November 2018).

Schiller, J., Castellsagué, X., Vaccine, S. G.- and 2012, undefined (2012) 'A review of clinical trials of human papillomavirus prophylactic vaccines', *Vaccine*, 30(Suppl 5), pp. F123–F138. Available at: https://www.sciencedirect.com/science/article/pii/S0264410X12009516%0A-here (Accessed: 23 October 2018).

Sertkaya, A., Wong, H.-H., Jessup, A. and Beleche, T. (2016) 'Key cost drivers of pharmaceutical clinical trials in the United States', *Clinical Trials*. SAGE PublicationsSage UK: London, England, 13(2), pp. 117–126. doi: 10.1177/1740774515625964.

Setiawan, D., Dolk, F. C., Suwantika, A. A., Westra, T. A., WIlschut, J. C. and Postma, M. J. (2016) 'Cost-Utility Analysis of Human Papillomavirus Vaccination and Cervical Screening on Cervical Cancer Patient in Indonesia', *Value in Health Regional Issues*. Elsevier, 9, pp. 84–92. doi: 10.1016/J.VHRI.2015.10.010.

Shamp, J. (2019) 'Merck Adding $680M, 425 workers to North Carolina Vaccine Production | North Carolina Biotechnology Center', *North Carolina Biotechnology Center*, July. Available at: https://www.ncbiotech.org/news/merck-adding-680m-425-workers-north-carolina-vaccine-production.

Smith, J., Lipsitch, M. and Almond, J. W. (2011) 'Vaccine production, distribution, access, and uptake', *The Lancet*. Elsevier, 378(9789), pp. 428–438. doi: 10.1016/S0140-6736(11)60478-9.

Toft, L., Storgaard, M., Muller, M., Sehr, P., Bonde, J., Tolstrup, M., Ostergaard, L. and Sogaard, O. S. (2014) 'Comparison of the Immunogenicity and Reactogenicity of Cervarix and Gardasil Human Papillomavirus Vaccines in HIV-Infected Adults: A Randomized, Double-Blind Clinical Trial', *Journal of Infectious Diseases*. Oxford University Press, 209(8), pp. 1165–1173. doi: 10.1093/infdis/jit657.

Tomljenovic, L. and Shaw, C. A. (2012) 'Too Fast or Not Too Fast: The FDA's Approval of Merck's HPV Vaccine Gardasil', *The Journal of Law, Medicine & Ethics*. SAGE PublicationsSage CA: Los Angeles, CA, 40(3), pp. 673–681. doi: 10.1111/j.1748-720X.2012.00698.x.

UN (2018) *LDCs at a Glance*, *United Nations*. Available at: https://www.un.org/development/desa/dpad/least-developed-country-category/ldcs-at-a-glance.html (Accessed: 9 January 2019).

UNICEF (2018) *Human Papillomavirus Vaccine: Supply and Demand Update*. Available at: https://www.unicef.org/supply/files/HPV_2_Status_Update.pdf.

Wheeler, C. M., Castellsagué, X., Garland, S. M., *et al.* (2012) 'Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial', *The Lancet Oncology*, 13(1), pp. 100–110. doi: 10.1016/S1470-2045(11)70287-X.

WHO (2018) *Global market study - HPV*. Geneva. Available at: https://www.who.int/immunization/programmes_systems/procurement/v3p/platform/module2/en/.

World Bank (2019) *World Bank Open Data*, *World Bank*. Available at: https://data.worldbank.org/ (Accessed: 29 January 2019).

Yin, Y. (2017) 'HPV vaccination in China needs to be more cost-effective.', *Lancet* . Elsevier,

390(10104), pp. 1735–1736. doi: 10.1016/S0140-6736(17)32606-5.

Zou, H., Tabrizi, S. N., Grulich, A. E., Garland, S. M., Hocking, J. S., Bradshaw, C. S., Morrow, A., Prestage, G., Cornall, A. M., Fairley, C. K. and Chen, M. Y. (2014) 'Early Acquisition of Anogenital Human Papillomavirus Among Teenage Men Who Have Sex With Men', *Journal of Infectious Diseases*, 209(5), pp. 642–651. doi: 10.1093/infdis/jit626.

Supplementary Material

Table B.1. Consumer price index (CPI) with base year 2015 and employed price index (PI) with base year 2018.

Observation date	CPI	PI*
2007-01-01	87.48	0.826
2008-01-01	90.84	0.857
2009-01-01	90.52	0.854
2010-01-01	92.00	0.868
2011-01-01	94.90	0.896
2012-01-01	96.87	0.914
2013-01-01	98.29	0.928
2014-01-01	99.88	0.942
2015-01-01	100.00	0.944
2016-01-01	101.26	0.956
2017-01-01	103.42	0.976
2018-01-01	105.94	1.00

* PI is given by CPI in a year with base year 2015 divided by CPI in 2018.

Source: (Federal Reserve Bank, 2018) and own calculation.

Table B.2. Detailed calculation for Table 11 of operating profits for different countries and country groups (a) 2007-2009, (b) 2010-2019 and (c) 2019-2027

a) Operating profits estimation, 2007-2009

			2007	2008	2009
USA	Price (US$)		131.55	131.72	138.03
	Variable costs	Low (US$)	1.00	1.00	1.00
		High (US$)	1.59	1.59	1.59
	# of doses (in millions)		10.42	9.50	7.25
	Profit	High (US$)	1,360.59	1,241.45	993.64
		Low (US$)	1,354.45	1,235.85	989.36
Other HIC	Price (US$)		45.96	45.96	45.96
	Variable costs	Low (US$)	1.00	1.00	1.00
		High (US$)	1.59	1.59	1.59
	# of doses (in millions)		9.18	8.38	6.70
	Profit	High (US$)	412.90	376.74	301.43
		Low (US$)	407.48	371.80	297.48
Total profit per year (in million US$)		High (US$)	**1,773.49**	**1,618.19**	**1,295.07**
		Low (US$)	**1,761.93**	**1,607.64**	**1,286.84**

b) Operating profits estimation, 2010-2019

			Year									
			2010	**2011**	**2012**	**2013**	**2014**	**2015**	**2016**	**2017**	**2018**	**2019**
U.S.	Price (US$)		137.61	126.16	127.99	130.76	139.17	148.96	163.57	164.47	164.47	137.61
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		6.32	8.18	10.66	11.54	10.13	10.81	11.39	9.75	8.84	9.10
	Profit (in million US$)	High	863.61	1,023.76	1,353.26	1,497.51	1,399.41	1,599.55	1,850.93	1,593.48	1,588.83	1,635.56
		Low	859.88	1,018.93	1,346.97	1,490.71	1,393.44	1,593.17	1,844.22	1,587.73	1,583.62	1,630.19
Other HIC	Price (US$)		45.96	45.96	45.96	45.96	45.96	45.96	45.96	45.96	45.96	45.96
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		9.34	12.70	7.61	5.86	5.10	3.98	4.27	5.91	5.95	6.12
	Profit (in million US$)	High	419.83	570.98	342.30	263.41	229.14	178.90	192.16	265.79	267.30	275.17
		Low	414.32	563.49	337.80	259.95	226.14	176.55	189.64	262.30	263.80	271.55
MIC	Price (US$)		20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		6.09	11.31	13.92	13.92	11.31	9.57	9.57	9.57	10.44	12.18
	Profit (in million US$)	High	118.88	220.78	271.73	271.73	220.78	186.81	186.81	186.81	203.80	237.76
		Low	115.29	214.11	263.52	263.52	214.11	181.17	181.17	181.17	197.64	230.58
GAVI	Price (US$)					4.69	4.69	4.69	4.69	4.69	4.69	4.69
	Variable costs (US$)	Low				1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High				1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		0.00	0.00	0.00	0.87	0.87	1.74	2.61	1.74	5.22	23.49
	Profit (in million US$)	High				3.21	3.21	6.42	9.62	6.42	19.25	86.62
		Low				2.69	2.69	5.39	8.08	5.39	16.17	72.76
Indonesia/India	Price (US$)								11.28	11.28	11.28	11.28
	Variable costs (US$)	Low							1.00	1.00	1.00	1.00
		High							1.59	1.59	1.59	1.59
	# of doses (in millions)		0.00	0.00	0.00	0.00	0.00	0.00	0.87	0.87	0.87	0.87
	Profit (in million US$)	High							8.94	8.94	8.94	8.94
		Low							8.43	8.43	8.43	8.43
Profit per year (in million US$)		**High**	**1,402.32**	**1,815.52**	**1,967.28**	**2,035.86**	**1,852.54**	**1,971.68**	**2,248.48**	**2,061.45**	**2,088.13**	**2,244.06**
		Low	**1,389.49**	**1,796.53**	**1,948.29**	**2,016.87**	**1,836.38**	**1,956.28**	**2,231.54**	**2,045.02**	**2,069.65**	**2,213.52**

c) Operating profit estimation, 2020-2027

			2020	2021	2022	2023	2024	2025	2026	2027
U.S.	Price (US$)		137.61	126.16	127.99	130.76	139.17	148.96	163.57	164.47
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		9.88	9.36	8.84	8.32	7.80	7.28	7.28	7.28
	Profit (in million US$)	High	1,350.38	1,172.05	1,123.15	1,080.10	1,078.26	1,077.67	1,184.07	1,190.63
		Low	1,344.54	1,166.53	1,117.94	1,075.19	1,073.66	1,073.38	1,179.77	1,186.33
Other HIC	Price (US$)		45.96	45.96	45.96	45.96	45.96	45.96	45.96	45.96
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		6.65	6.30	5.95	5.60	5.25	4.90	4.90	4.90
	Profit (in million US$)	High	298.75	283.03	267.30	251.58	235.86	220.13	220.13	220.13
		Low	294.83	279.31	263.80	248.28	232.76	217.24	217.24	217.24
MIC	Price (US$)		20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		13.05	13.05	13.05	13.05	13.92	14.79	14.79	14.79
	Profit (in million US$)	High	254.75	254.75	254.75	254.75	271.73	288.71	288.71	288.71
		Low	247.05	247.05	247.05	247.05	263.52	279.99	279.99	279.99
GAVI	Price (US$)		4.69	4.69	4.69	4.69	4.69	4.69	4.69	4.69
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		34.80	26.97	28.71	31.32	21.75	27.84	26.10	25.23
	Profit (in million US$)	High	128.33	99.45	105.87	115.49	80.20	102.66	96.24	93.04
		Low	107.79	83.54	88.93	97.01	67.37	86.23	80.84	78.15
Indonesia/India	Price (US$)		11.28	11.28	11.28	11.28	11.28	11.28	11.28	11.28
	Variable costs (US$)	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		0.87	13.92	25.23	23.49	24.36	21.75	20.01	18.27
	Profit (in million US$)	High	8.94	143.12	259.40	241.51	250.45	223.62	205.73	187.84
		Low	8.43	134.90	244.51	227.65	236.08	210.78	193.92	177.06
China	Price (US$)				159.38	159.38	159.38	159.38	159.38	159.38
	Variable costs (US$)	Low			1.00	1.00	1.00	1.00	1.00	1.00
		High			1.59	1.59	1.59	1.59	1.59	1.59
	# of doses (in millions)		0	0	0.87	2.61	3.48	3.48	4.35	6.09
	Profit (in million US$)	High			137.79	413.36	551.15	551.15	688.93	964.50
		Low			137.27	411.82	549.09	549.09	686.36	960.91
Profit per year (in million US$)		**High**	**2,041.14**	**1,952.39**	2,148.26	**2,356.79**	**2,467.65**	**2,463.94**	**2,683.81**	**2,944.85**
		Low	**2,002.65**	**1,911.33**	**2,099.49**	**2,307.00**	**2,422.48**	**2,416.72**	**2,638.13**	**2,899.68**

Source: Own calculations based on Tables 3, 4, 6a, 10.

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Abstract
Human papillomavirus (HPV) is responsible for almost all of the 530,000 new cases of cervical cancer and approximately 266,000 deaths per year. HPV vaccination is an integral component of the World Health Organization's global strategy to fight the disease. However, high vaccine prices enforced through patent protection are limiting vaccine expansion, particularly in low- and middle-income countries. This raises the question of the patent buyout price for Merck's HPV vaccines (Gardasil-4 and 9), which hold 87% of the global HPV vaccine market. It also raises the question about the market power from patent protection, that we assess by estimating the ratio of R&D costs for Gardasil and its patent value. We estimate the patent buyout price for various groups of countries and in total. The estimated global Gardasil patent buyout price in 2020 is between US$ 15.33 – 18.32 billion (in 2018 US$), the estimated present discounted value of the profit stream for 2007-2028 amounts to US$ 22.29 – 33.08 billion, and the estimated total R&D cost is between US$ 1.10 – 1.21 billion. Thus, we arrive at a ratio of R&D costs to the patent value of the order of 3-5%, suggesting that patent protection provides Merck with extraordinarily strong market power.

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