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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

Abstract

Human papillomavirus (HPV) is responsible for almost all of the 570,000 new cases of cervical cancer and approximately 311,000 deaths per year. HPV vaccination is an integral component of the World Health Organization's (WHO) 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. By limiting market power, patent buyouts could reduce vaccine prices and raise HPV vaccination rates while keeping innovation incentives. We estimate the global patent buyout price as the present discounted value (PDV) of the future profit stream over the remaining patent length for Merck's HPV vaccines (Gardasil-4 and 9), which hold 87% of the global HPV vaccine market, in the range of US$ 15.6–27.7 billion (in 2018 US$). The estimated PDV of the profit stream since market introduction amounts to US$ 17.8–42.8 billion and the estimated R&D cost to US$ 1.05–1.21 billion. Thus, we arrive at a ratio of R&D costs to the patent value of the order of 2.5–6.8%. We relate this figure to typical estimates of the probability of success (POS) for clinical trials of vaccines to discuss if patent protection provides Merck with extraordinarily strong price setting power.

JEL-Codes: I180, L120, L650.

Keywords: Human Papilloma Virus (HPV) vaccine, market power, patent buyout price, patent value, R&D costs.

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1. Introduction

Cervical cancer, a disease mainly caused by human papillomavirus (HPV), is the fourth most common type of cancer in women with approximately 570,000 new cases and 311,000 deaths per year globally (1–3). By 2030 cervical cancer is projected to cause around 474,000 deaths in women annually. 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 (4,5).

The vast majority (95%) of deaths caused by cervical cancer and around half of the world's new cases are in low-income countries (LIC) and middle-income countries (MIC) (6–9). The highest age-standardized incidence rate is observed in countries in South Asia and Sub-Saharan region, where the vast majority of LIC and MIC are located (10). The high prevalence of cervical cancer in these countries is caused by low coverage of HPV vaccination. In 2017 only 6% of LIC and 8% of lower-middle income countries introduced the new and effective HPV vaccines (11).

High vaccine prices, enabled by patent protection, is considered one of the main factors limiting the expansion of HPV vaccination in developing countries (12,13). 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 (14,15).

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 (16). For lowering prices of pharmaceuticals and extending access, pull programmes that limit market power of pharmaceutical companies entail larger potential.

This study focusses on patent buyouts by government agencies to supply medicines at lower costs and make them affordable to poorer countries via licensing production to many competitors (17). We estimate the patent buyout price as the present discounted value (PDV) of incumbent's expected future profits over the remaining patent length for two HPV vaccines, Gardasil-4 and Gardasil-9, from 2020 onwards. We use the current and past pricing strategies in different markets by patent holder Merck jointly with sales data including future predictions provided by (18). Data on variable costs for materials, labor and capital are adapted from (12). Our measure for fixed costs include overhead costs derived from data provided by (12) and marketing expenditure based on acquired data from 'The Nielsen Company'. We come up with regional estimates for operating profits and a global patent buyout price. 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, focussing the patent buyout on these groups of countries may be infeasible. First, pharmaceutical companies may be reluctant to this solution because they fear parallel imports or a black market for generic drugs. They may also fear public debate on prices in high-income countries (HIC) or reference pricing in health systems based on the global market, once local supply by generic manufacturers at low prices make high price-cost margins in HIC transparent (19).

We also estimate the global value of the Gardasil patents at market entry, using a similar methodology as for deriving the patent buyout price, and derive estimates of R&D costs by identifying each clinical trial sponsored by Merck on www.clinicaltrial.gov and a literature search. We calculate the R&D costs based on previously estimated costs per subject (15), clinical trial site, and study (20). 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 develop virus-like particle (VLP) technology used in the vaccine in the early 1990s (21). Merck later acquired the licenses and took the then vaccine candidate to clinical testing (21).

We compute the ratio of estimated R&D costs for clinical trials to the patent value (PDV of the stream of profits from market entry to patent expiry). In theory, this ratio is the probability of success (POS) in finding an innovation that is required to just cover the R&D costs in expected value (22). We thus compare our estimated ratio of R&D costs to the value of the Gardasil patents with POS estimates in the literature of moving vaccines for infectious diseases successfully from Phase I to approval. This strategy allows us to discuss whether the patent system gives vaccine producers more market power than needed to serve the goal of providing incentives to start clinical trials for a particular vaccine candidate.

Our estimated global patent buyout in year 2020 for Gardasil vaccines is in the range of US$ 15.6–27.7 billion (in 2018 US$), depending on assumed real annual return to investment in alternative uses, price estimates, and cost estimates. The patent value, we estimate between US$ 17.8–42.8 billion. These high values reflect our findings of high price-cost margins which could be around 100 for the U.S. and China and still well above 10 in MIC. The estimated R&D costs for both Gardasil vaccines combined lie in the range between US$ 1.05–1.21 billion. These figures imply a ratio of R&D costs and the patent value between 2.5–6.8%. We will argue that this figure is considerably lower than we would expect from the estimated POS for vaccines from Phase I to approval in the literature, suggesting that the patent holder earns extraordinarily high profits.

Our contribution to the literature is fourfold. First, we provide an alternative to existing proposals of patent buyouts for pharmaceuticals that is based on available data on revealed pricing strategies, past sales, predictions on future sales, and costs. The most prominent idea so far is to determine the patent buyout value by a second-price auction (17). In order to incentivize bidders to reveal their true valuation, with small probability the patent would not be put into the public domain but awarded to the winning bidder. To incentivize patent holders to participate, the government would pay a mark-up over the winning bid. To the best of our knowledge, the idea has yet not been applied.

Another mechanism for designing a patent-buyout presumes that prices can be manipulated to infer the demand function for a pharmaceutical (23), mitigating applicability. In our approach, non-profit institutions or government agencies as potential buyers would base their offer for the patent buyout price on the estimated (remaining) value of the patent.

Second, we refine attempts to suggestively relate sales revenues and R&D costs (24). Motivated by economic innovation theory, we rather estimate the ratio of R&D costs to the patent value and compare it with POS estimates for developing an effective vaccine against infectious diseases in the literature. Applying that procedure at large scale beyond the specific HPV vaccines we consider may alter price negotiations for prescription drugs in health systems and may ultimately call for adjustment of the patent system.

Third, we propose how to generate estimates on R&D costs without using self-reported data. The literature arrives at estimates for drug development in the range of US$ 161 million to US$ 1.8 billion (25). However, estimates of R&D costs from confidential sources such as self-reported R&D costs from pharmaceutical companies and estimates of industry experts are impossible to assess for accuracy, representativeness, or sensitivity to outliers. (15) estimated the R&D costs of Rotavirus vaccines, RotaTeq (Merck) and Rotarix (GlaxoSmithKline-GSK), and found that they were considerably lower than the average values cited in the literature. Furthermore, many pharmaceutical companies receive public and non-profit funds that confound the estimates on the companies' own R&D investments (25).

Fourth, estimating patent values requires to re-estimate manufacturing costs of Gardasil provided by (12) by explicitly distinguishing variable costs and fixed costs. Importantly, we also include marketing expenditure as additional component to fixed costs.

1.1 Background: Vaccines for HPV

HPV is a group that encompasses over 100 viruses and 15 of them have been shown to be responsible for almost all cases of cervical cancer: HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68, 73, and 82 (26). 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 (27). 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 (28). In Africa, HPV 16 and 18 are responsible for 43.7-90.2% of the invasive cervical cancer cases (29).

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 (30). 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 (31).

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 (32). Thus, 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. Both combine newly developed adjuvants, delivery vectors and knowledge of the tumour microenvironment (32). However, it may take considerable time until effective HPV therapeutic vaccines reach the market (33).

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 (32,34). 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 types (33). 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 (33). 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 (35).

Vaccination is an integral part of the WHO global strategy to combat HPV infections and related diseases (9). According to WHO recommendations, girls aged 9-14 years should receive two doses of Gardasil-4 whereas older age groups receive three doses (9). It is too early to assess the impact of Gardasil-4 and Cervarix vaccination on prevalence of invasive cervical cancer 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 (32). 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 (27,36). 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 (37).

It is estimated that 70-80% of females in pre-pubertal age have to be vaccinated in order to achieve herd immunity (38). 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) (32). In these countries, it has been estimated that HPV vaccination has the potential to reduce the lifetime risk of cervical cancer by 31-60% (39).

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 the subsequent steps required to bring the vaccine to the market (21). Merck’s Gardasil-4, the first VLP based vaccine, was patented in the U.S. in 1998 and introduced in the market in 2006 (40). 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 (21). Table 1 shows global revenues of Gardasil and Cervarix between 2006 and 2018, suggesting that Gardasil has dominated with an average market share of 87% in the period 2007-2018. For this reason and because it is effective against more HPV types, we focus on Gardasil.

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

	Gardasil (in million US$)*	**Cervarix (in million US$)****
2006	234.8	0
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, 2018a, 2018b). ** Original revenues are in Great Britain Pound (£). We used the exchange rate of the respective year on July 2 (43) to calculate the revenue in US$.

Sources: Merck (35,44–48), GSK (49–54).

There is no centralized database to obtain information about the status of the various patents related to a particular vaccine in different countries/regions. In the U.S., Gardasil patents expire in 2028, and similarly in other advanced countries (35,55). We focus on patent buyout prices for all country groups and total patent values until 2028.

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 (18,56). 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 (57–60).

1.2 The benefit of HPV vaccine patent buyout

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. Patents like those for HPV vaccines provide intellectual property protection that bars entry of generic competitors for an extended period of time, therefore awarding monopoly price setting power. Because inventions use prior knowledge that is protected by patents, it is *a priori* not evident that patents are stimulating innovation (61). One of the strategies to counter patents is to challenge them on court. However, it is a long and expensive process that most small and medium sized companies cannot afford. Another strategy is to work around patents. This, however, is very challenging because patents often cover various stages of the vaccine development and manufacturing process (62). Working around patents increases uncertainty and costs, thus constituting a barrier for vaccine development.

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 (62). There is evidence that TRIPS limited access to pharmaceuticals formerly manufactured by local suppliers (19). However, under the agreement, the least-developed countries (63) are not obliged to provide patent protection in general until 2021, and on medicines (including vaccines) specifically until 2033 (64).

Brazil, India and China have a large generic pharmaceutical industry supplying 64% of vaccines purchase by UNICEF and 43% of vaccines procured by GAVI (21). In addition to manufacturing generic vaccines, these countries are also capable of developing HPV vaccines themselves (21). 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 (62).

WHO has launched a global effort to eliminate cervical cancer by promoting introduction of HPV vaccination in all countries (56). Accordingly, 48 GAVI-supported countries announced plans to introduce multi-age cohort HPV vaccination and protect approximately 40 million girls by 2020 (56). However current manufacturers could not match the demand leading to supply shortages and the goal been reduced to protect only 14 million girls (65). Moreover, the introduction of HPV vaccination in China, India and Indonesia adds significantly to global demand. From 2023 the demand for HPV vaccines is likely to exceed production capacity (18).

Another factor limiting the expansion of HPV vaccination are the high prices of HPV vaccines that are prohibitive to GAVI and PAHO supported LIC and MIC (13). To date, 74% of the 81 countries that have introduced the HPV vaccination self-procure the vaccines (56).

The discussion strongly suggests that the entrance of new manufacturers is crucial to ensure sufficient supply and lower HPV vaccine prices, thus increasing static economic efficiency by mitigating price setting power of the incumbent (17). Given the currently high price-cost margins we display in this research, patent buyout for the market leader Gardasil-4 and Gardasil-9 that puts the right to manufacture and sell the vaccine into public domain could allow fast entry of competitors and development of new and less expensive technology (i.e. plant-based production). Importantly, a patent buyout price equal to the estimated PDV of the expected stream of future profits would most likely fully compensate the innovator for the expected loss in profits from market transactions while keeping incentives for future innovators unchanged (i.e. not compromising dynamic efficiency).

Despite these arguments in favor of the patent buyout at the suggested price, we do not aim to calculate the net social benefit from the patent buyout because of several difficulties to predict the entry response of generic manufacturers and the price responses by the patent holder. First, for some period of time after the buyout, Merck would likely continue to be the major supplier and prices may remain significantly above marginal costs. It is also plausible that some LIC and MIC countries would choose to postpone introducing HPV vaccination (or postpone scaling up pilot programs) until after generics enter the market, if they knew it was imminent. Likewise, GAVI and the PAHO revolving fund would aim at negotiating lower prices.

2. Methodology and data

We first propose our methodology to estimate the patent buyout price and to assess the extent of price setting power in the market of HPV vaccination. We then discuss the data and assumptions for our estimations.

2.1 Theoretical considerations on the patent buyout price

Our first goal is to estimate the PDV of the expected future stream of real profits for the vaccine Gardasil, starting from year $\underline{T}$, i.e. year 2020 this gives us the patent buyout price (with caveats discussed in Section 4) for the vaccine Gardasil under the assumption of risk-neutrality. Arguably, large pharmaceutical companies like Merck can be considered risk-neutral as they are owned by shareholders that can hold diversified asset portfolios. Moreover, they have diversified product portfolios and can diversify R&D effort. By contrast, a (small) risk-averse company facing market uncertainty would agree to a patent buyout price that is lower than the PDV of expected future profits. To calculate the time path of profits, we need estimates for sales prices, variable costs, and fixed costs. We assume that the variable 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:

- user costs of physical capital (equipment, building, pipes),
- costs for materials needed to express and purify the VLPs of the targeted HPV types,
- costs for filling and packaging (staff and material),
- costs for operating labor (manufacturing operators, quality assurance, and quality control operators).

Fixed costs consist of:

- overhead labor costs for managing and supervising the manufacturing process in the facilities used for producing the vaccine,
- labor costs for maintaining the facilities and equipment,
- marketing expenditure (direct-to-consumer advertising and promotion on health providers).

We follow (12) to treat maintenance costs as fixed costs, albeit we checked that our results are not significantly affected by this choice. We depart from (12) by modelling capital investments as variable rather than fixed costs to account for the possibility of alternative uses ("user costs of capital"), as is standard in economics.

Legal costs for patent defence, patent infringement disputes, product liability litigations, commercial litigations, government proceedings or environmental matters should generally be considered as fixed costs. Merck gives a detailed account of these costs in its annual reports. However, so far, no legal proceedings or costs were reported for Gardasil-4 and Gardasil-9. Also notably, R&D expenditures are incurred *ex ante* and thus cannot be considered being part of the fixed cost (66).

That said, we still miss some labor-intensive fixed cost components that are private information like building relations with suppliers of material, training costs and costs for developing the manufacturing to scale process and packaging design. There is reason to assume, however, that in the present context these costs are small. First, large scale manufacturing of VLP based vaccines was already being done in the 1990s and early 2000s for a variety of VLPs vaccines against HEV, influenza, BTV, rotavirus and PPV (67). All the techniques, technologies and equipment were routinely used at the time when Gardasil was being developed. Moreover, for manufacturing its other vaccines Merck had already established supplier relations for the bulk of the material components to produce Gardasil.

We also miss distribution costs. However, the vast majority of distribution costs are covered by government and NGO's. In the U.S., the Centers for Disease Control (CDC) Vaccine Supply and Assurance Branch (VSAB) oversees all aspects of its vaccine purchase and distribution in the country

(68). In the EU, the most common strategy is for the manufacturers shipping vaccines to distribution centres and wholesalers, who are then responsible for the distribution within the country (69). In GAVI supported countries the distribution is carried by governments and the various partnering NGOs, i.e. WHO, UNICEF, etc. (69).

We index the country (group) in which Gardasil is sold by $j \in \{1,2,\dots,J\}$ and denote the time horizon by T (U.S. patent expiry year 2028 in our application). We use information about the time paths of the predicted future number of doses sold at the regional level, $\{y_{jt}\}_{t=\underline{T}}^{T}$. We deflate all prices and costs to its 2018 US$ value for obtaining the time series of real profits. For data availability reasons, we assume that the variable unit cost is time-invariant in *real* terms. In year *t*, operating profits from sales to country group *j* are then given by

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

where p_{jt} and y_{jt} denote sales prices and number of doses in region *j* and year *t*, respectively, and *c* the variable costs per dose.

Based on (1), we can then estimate the present discounted value (PDV) of the stream of operating profits from period $\underline{T}$ onwards in country group *j* until time T as

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

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 range of 3–7%.

Fixed costs are typically not region-specific, as production takes place in few facilities and the product is shipped from there. We denote real global fixed costs in year *t* by f_t and the PDV of the fixed cost stream from period $\underline{T}$ until time T by

$$F(\underline{T}) \coloneqq \sum_{t=\underline{T}}^{T} \frac{f_t}{(1+r)^{t-\underline{T}}}. \tag{3}$$

Thus, the global patent buyout price in year $\underline{T}$ for the considered regions is given by

$$V(\underline{T}) \coloneqq \sum_{j=1}^{J} \Pi_j(\underline{T}) - F(\underline{T}). \tag{4}$$

We assume that both variable unit cost c and fixed costs F are the same for Gardasil-4 and Gardasil-9.

Arguably, buying out a patent in $\underline{T}$ at the PDV of future profits, $V(\underline{T})$, fully compensates the patent holder for its profit losses associated with lower price setting power and is thus incentive-compatible.

2.2 Required probability of success (POS) to break even

We also aim to estimate the patent value from the perspective of the date introduced in the market and compare it with R&D costs. Gardasil-4 was introduced in September 2006, i.e. 2007 was the first full year Gardasil was sold. To generate conservative estimates of the patent value and since we do not have price information for 2006, we neglect profits for 2006 and include marketing costs for 2006 in total fixed costs for 2007.

Denoting the first full year of market introduction $s \leq \underline{T}$, the total patent value is given by $V(s)$. If the market for innovations is characterized by free entry and firms are risk-neutral, the expected value of an innovation (accounting for a potentially high risk of R&D failure) equals R&D costs (22). Formally, let μ denote the POS in the innovation process, such that $\mu \cdot V(s)$ is the expected patent value (in case of R&D failure, with probability $1 - \mu$, profits are zero). A firm is incentivized to conduct the innovation project as long as $\mu \cdot V(s) \geq R\&Dcosts$. The POS required to break even in expected value is given when the inequality is binding. It is defined as

$$\mu_0 := \frac{R\&D\ costs}{V(s)} \tag{5}$$

Our data allows us to estimate the right-hand side of eq. (5). To assess market power, we compare the estimated μ_0 with typical estimates of the average POS for clinical trials of other vaccines reported in the literature. Higher price setting power would increase $V(s)$ and thus decrease μ_0. A value of μ_0 that is considerably lower than the average POS found for other vaccines could therefore indicate excessive price setting power of the patent holder.

In our context of HPV vaccines, the POS is the cumulative probability of moving from the three phases of clinical trials to approval. Recall that Gardasil-9 was an improvement of Gardasil-4, the first VLP-based HPV vaccine approved by the FDA (70). Gardasil-4 and Gardasil-9 are typically not sold in parallel within the same region. Thus, for obtaining μ_0, we sum up both the PDV of profits from both Gardasil-4 and Gardasil-9 since market introduction until patent expiry when computing $V(s)$, the denominator of (5), and sum up the R&D costs for both to compute the numerator.

2.3 Data and assumptions

We now outline the data sources, how we extrapolate missing information, and how we deal with measurement problems and uncertainty with respect to future values. We convert all monetary variables to 2018 US$, using the U.S. consumer price index (71). Detailed statistics and derivations based on the assumptions to extrapolate missing data are relegated to the "Supporting Information" on the article.

2.3.1 Data for operating profits

According to eq. (1), calculating regional operating profits requires estimates of regional sales prices (p_{jt}), regional number of doses sold (y_{jt}), and variable unit cost (c). The prices of HPV vaccines vary greatly depending on procurement agreement and countries' income (9). Merck and GSK have agreements with organizations such as GAVI, that mediates purchase of vaccine to developing countries in Africa and Asia and PAHO, that mediates vaccine purchase to LIC and MIC in South and Central America (72,73). When Gardasil-4 was introduced in the U.S. market, the median price was US$ 96.75 per dose to CDC funded programs and US$ 120.5 per dose to the private sector. It was the most expensive vaccine in the world at the time (42,74). In 2018, Gardasil-9 was sold at a price of US$144.2 and US$ 217.1 to CDC and the private sector, respectively (Table S2) (42). The median U.S. private sector price for Gardasil-9 in 2016 was about twice as high than in other HIC and about 25% higher than in China (75,76). The median Gardasil-4 price in 2016 was about US$ 20 in MIC (9), US$ 4.50 for sales mediated by GAVI (9) and in-between in India (77) and Indonesia (78) (Table S1). We assume that from 2019 onwards regional prices stay the same as the latest one observed (in 2018 US$), taking Gardasil-9 prices for HIC and China and Gardasil-4 prices for the other regions. Due to the price difference between the U.S. and other HIC, we treat the U.S. as separate region, assuming that half of the units sold in the U.S. are mediated by CDC funded programs and the other half by the private sector.

Through its own databases and interviews with stakeholders (i.e. national vaccination programme managers, industry leaders and experts), (18) estimated the number of HPV doses sold between 2010-2017 by country group and forecasted quantities for 2018-2027, however, without distinguishing the U.S. and other HIC. To break down the number of units sold between the U.S. and other HIC, we use the global sales revenues in Table 1 and the revenue for the U.S. for 2015-2017 that is additionally available in Merck's annual report (79) to find that about three quarters of the global sales revenue is earned in the U.S. (Table S3a). Assuming that this has also been the case in 2007-2014, information on prices and revenues for the U.S. allow us to distil the number of doses (revenue divided by price) in the U.S. (Table S3b). Moreover, although (18) did not estimate the number of doses sold from 2007-2009, we obtain the number of doses sold in other HIC from the additional information that in this time period Gardasil was sold in HIC only (Table S3c). For the period 2018-2027, we assume that the share of the number of doses in the U.S. within HIC is the same as the average in 2007-2017 (about 60%) (Table S4). We suppose that the number of doses in patent expiry year 2028, for which we do not have data, is the same as predicted for 2027.

We account for measurement problems of past vaccine doses' sales and uncertainty in the predictions for future sales by creating a "low" and "high" scenario by deducting and adding 20% of the sales of doses sold to the middle estimates that we derive by the outlined procedure (Tables S5a and S5b). For instance, the predictions are based on the current dosage recommendation for HPV vaccination. However, a recent clinical trial in India showed that a single dose of Gardasil induces a robust and sustained immune response against HPV 16 and 18 (although slightly inferior to those induced by the standard 3-doses vaccination) and the antibody levels were stable over a four-year period (80).

Interestingly, the cumulative incidence of HPV 16 and 18 infections was similarly low in those that received one, two or three doses of Gardasil (80). If more studies show further evidence that a single dose is sufficient to protect against HPV-16 and 18 infection, then the forecasted number of doses required could be significantly lower. Likewise, it is possible that future demand is underestimated because of regional changes in health strategies.

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. The manufacturing process has four steps: cultivation, extraction, purification type-specific VLPs from L1-recombinant producer cells, filling and packaging (12). Associated variable costs consist of annual costs for labor, per-batch costs for raw materials, and capital costs. We take over the "low" and "high" estimate of annualized capital costs (for building, equipment and pipes) from (12) (Table S6a). Based on the average number of doses sold between 2010-2017, we obtain the unit variable capital costs of Gardasil-4 (Table S6b). Similarly, we use the estimate of the unit costs for materials provided by (12). The "high" estimate is based on the life science and technology companies list prices in 2013 (in 2018 US$) and the "low" estimate on a 40% discount on the cost for materials (Table S7). Regarding labor costs, we deviate from (12) by distinguishing variable and fixed labor costs, taking over their range of salary estimates and required staff for the different occupations. We treat salaries of manufacturing operators, quality assurance operators, quality control operators and fill/pack staff per unit as variable costs (Table S8).

2.3.2 Data for fixed costs

Fixed manufacturing costs consist of management and supervisor overhead costs, and the costs of maintenance of the facility, and the equipment according to 'Good Manufacturing Practices' guidelines (electricity, heating, cooling and operation of the machinery) (Table S10a). As such "factory and administrative overhead" costs are not readily available, we take over the assumption in (12) that they correspond to 45% of the total cost for other personnel and material (Table S10b).

The second component of fixed costs are marketing expenditures. We obtained the time series of Merck's direct-to-consumer advertising (DTCA) expenditure to promote Gardasil-4 and Gardasil-9 in the U.S. since market entry from 'The Nielsen Company'. We use their additional information that DTCA spending in the U.S. is 90% of the global spending and create two scenarios for the missing marketing expenditure of health care providers (Table S11). First, for the low-cost scenario we assume that 2/3 of global marketing spending is on DTCA. The scenario is motivated by the evidence that Merck's marketing strategy focused to a large extent on raising awareness of the general public of the risk of cervical cancer. Gardasil was marketed as vaccine against such cancer, aiming to increase demand from consumers for HPV vaccination (81). Second, for the high-cost scenario, we assume that global marketing spending on health care providers is twice as high than marketing spending on DTCA. The range for the marketing cost split is consistent with evidence on other pharmaceuticals (82). Our data for DTCA spending suggests that marketing expenditures decline quickly over the life-cycle of a new vaccine. We assume that annual spending from year 2020 onwards equals, in real terms, the average annual spending in the last three available years (2017-2019).

2.3.3 Data for R&D investment

The elements discussed so far allow us to calculate the total patent value, $V(s)$, according to eqs. (1)-(4). To apply eq. (5), we relate these to R&D costs. We add the costs of clinical trials (phase I to III). Notably, we do not include the costs of clinical development because it was mainly performed by academic institutions (21). To estimate the costs of each clinical trial we performed a literature review coupled with a search in www.clinicaltrial.gov to identify the Gardasil related clinical trials sponsored by Merck in each phase. To calculate the costs on subjects (set-up, recruitment, administration and support) for each clinical phase we use the phase-specific estimates of costs per subject in (15) (Table S12) and multiply them with the number of subjects identified in www.clinicaltrial.gov. In addition to subject-related costs, there are site costs (for recruitment and retention of subjects as well as administrative and site monitoring) and study costs (data collection and management, institutional review board approvals and amendments, source data verification, overheads and other costs) (Table

S13). Both site and study costs per trial in the three phases are taken from (20) and multiplied with the number of clinical trials in each phase for Gardasil-4 (Table S14a) and Gardasil-9 (Table S14b).

According to www.stats.oecd.org, capital R&D costs in business enterprises for "basic pharmaceutical products and pharmaceutical preparations" are typically around 10% of non-capital R&D costs (e.g. 10.4% in the UK 2016, 10.1% in Germany 2017, 11.3% in Japan 2018; retrieved July 19, 2020). We add 10–15% to the subject-related, site and study costs to account for R&D capital costs.

3. Results and discussion

3.1 Operating profits

Based on the assumptions and data presented in Section 2.3, Table 2 displays the middle estimates for number of doses sold in different (groups) countries between 2007-2017 and forecasted until 2027. The forecasts in Table 2 suggest that annual future sales are slightly increasing in HIC and MIC. Globally, they more than triple because of sales increases in emerging markets and those mediated by GAVI.

Table 3 displays the range of variable costs per dose (1.00-1.59 US$) and its composition. We see that costs for materials, filling and packaging are responsible for about one third of variable costs. Filling and packaging represents almost 60% of these costs, being composed of the wholesale cost of the vial, cap and stopper (for single-dose packaging) at US$ 0.21 per dose plus secondary packaging materials at US$ 0.10 per dose (12). About one quarter of variable costs are labor earnings. The remaining costs are capital costs (about half for building and half for equipment).

It is interesting to look at price-cost margins. Even based on the high estimate for variable costs, the mark-up factor (price divided by unit variable costs) in 2016 is around 100 for the U.S. and China, twelve in MIC and almost three for sales mediated by GAVI.

Table 2. Number of Gardasil doses sold in different countries and country groups between 2010-2017 and forecasted quantities until 2027 (middle estimates), in millions.

Year	HIC total	U.S.	Other HIC	MIC	GAVI	India/ Indonesia	China	Total
2007	19.60	10.42	9.18	0.00	0.00	0.00	0.00	19.60
2008	17.88	9.50	8.38	0.00	0.00	0.00	0.00	17.88
2009	13.95	7.25	6.70	0.00	0.00	0.00	0.00	13.95
2010	15.66	6.32	9.34	6.09	0.00	0.00	0.00	21.75
2011	20.88	8.18	12.70	11.31	0.00	0.00	0.00	32.19
2012	18.27	10.66	7.61	13.92	0.00	0.00	0.00	32.19
2013	17.40	11.54	5.86	13.92	0.87	0.00	0.00	32.19
2014	15.23	10.13	5.10	11.31	0.87	0.00	0.00	27.41
2015	14.79	10.81	3.98	9.57	1.74	0.00	0.00	26.10
2016	15.66	11.39	4.27	9.57	2.61	0.87	0.00	28.71
2017	15.66	9.75	5.91	9.57	1.74	0.87	0.00	27.84
Subtotal (2007-2017)	**133.55**	**78.77**	**54.77**	**85.26**	**7.83**	**1.74**	**0.00**	**228.38**
2018*	14.79	8.84	5.95	10.44	5.22	0.87	0.00	31.32
2019*	15.23	9.10	6.12	12.18	23.49	0.87	0.00	51.77
2020*	16.53	9.88	6.65	13.05	34.80	0.87	0.00	65.25
2021*	15.66	9.36	6.30	13.05	26.97	13.92	0.00	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	26.10	20.01	4.35	77.43
2027*	12.18	7.28	4.90	14.79	25.23	18.27	6.09	76.56
Subtotal (2018-2027)	**140.51**	**84.02**	**56.48**	**133.11**	**251.43**	**149.64**	**20.88**	**695.57**

Source: Own calculations displayed in Tables S1-S4.

Table 3. Variable costs for manufacturing Gardasil, in 2018 US$.

	Low estimate	High estimate
Costs for materials, filling and packaging per million doses	323,947.53	539,912.55
Variable labor 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 displayed in Tables S6b-S8.

Table 4. Estimated PDV of the stream of operating profits (in million 2018 US$) for the periods 2020-2028 and 2007-2028, applying eq. (2).

	Interest rate (r)	Estimate	2020-2028	2007-2028
U.S.	0.03	High	14,210.23	27,584.81
		Low	9,442.37	18,319.64
	0.05	High	13,297.34	23,009.99
		Low	8,835.78	15,280.53
	0.07	High	12,488.32	19,507.41
		Low	8,298.20	12,953.80
Other HIC	0.03	High	4,987.46	7,881.96
		Low	3,304.06	5,203.35
	0.05	High	4,667.06	6,541.63
		Low	3,091.80	4,316.87
	0.07	High	4,383.11	5,531.79
		Low	2,903.69	3,649.14
MIC	0.03	High	2,604.31	3,801.51
		Low	1,683.73	2,457.74
	0.05	High	2,417.15	3,045.89
		Low	1,562.73	1,969.22
	0.07	High	2,251.97	2,477.06
		Low	1,455.94	1,601.46
GAVI	0.03	High	983.84	786.55
		Low	550.95	440.47
	0.05	High	919.39	581.95
		Low	514.86	325.89
	0.07	High	862.34	434.61
		Low	482.91	243.38
Indonesia and India	0.03	High	1,807.90	1,258.95
		Low	1,136.10	791.14
	0.05	High	1,669.09	906.87
		Low	1,048.87	569.89
	0.07	High	1,545.54	658.69
		Low	971.23	413.93
China	0.03	High	4,342.43	2,938.32
		Low	2,884.17	1,951.58
	0.05	High	3,902.78	2,048.96
		Low	2,592.16	1,360.88
	0.07	High	3,517.86	1,440.22
		Low	2,336.50	956.57
TOTAL	0.03	High	28,936.17	44,252.10
		Low	19,001.38	29,163.92
	0.05	High	26,872.81	36,135.28
		Low	17,646.20	23,823.28
	0.07	High	25,049.13	30,049.77
		Low	16,448.47	19,818.28

Source: Own calculations based on Table S9.

We derive two estimates for regional operating profits. The "high" estimate combines the 20% upward deviation from the middle estimates of the number of doses in Table 2 with the "low" unit cost estimate in Table 3 (regional prices are given in Tables S1 and S2), applying eq. (1), and vice versa for the "low" estimate. Based on those, we apply eq. (2) to derive the PDV ranges of the future (2020-2028) and total (2007-2028) stream of operating profits. Table 4 presents the results for three interest rates, r=0.03, r=0.05 and r=0.07. We estimate the PDV of future operating profits from the perspective of year 2020 in the range of US$ 16.45–28.94 billion, and the total PDV of the stream operating profits from the perspective of year 2007 in the range of US$ 19.82–44.25 billion. Reflecting the comparatively high sales prices in the U.S., half of the future profits are earned in the U.S. The profit share earned in the U.S. is even higher when considering the time period 2007-2028, as the sales share in the U.S. market was higher in the past than predicted for the future, reflecting market expansion to less developed countries.

3.2 Fixed costs

We next derive the PDV of fixed costs by applying eq. (3). Table 5 lists the estimated annual manufacturing fixed costs. These are based on the labor compensation for the required number of directors, managers and supervisors for the current factory in Durham, North Carolina, as presented in (12) and on the "factory and administrative overhead", corresponding to 45% of the total cost for personnel and material (Section 2.3).

Table 5. Annual manufacturing fixed costs, in million 2018 US$.

	Low estimate	**High estimate**
Fixed costs for directors, managers, supervisors	1.000	1.436
Factory and administrative overhead	7.740	11.963
Total fixed costs per factory per year (2007-2021)	**8.740**	**13.399**
Total fixed costs in 3 factories per year (2022-2028)	**26.221**	**40.196**

Source: Own calculations displayed in Tables S10a and S10b.

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 (83). Since the additional factories will also be based in the U.S., we assume that the costs are the same in these additional factories. Thus, current fixed manufacturing costs are multiplied by three to obtain an estimate for fixed manufacturing costs from 2022 onwards.

Based on DTCA spending data for the Gardasil vaccines in the U.S. (90% of global DTCA spending), the assumptions on marketing spending on health providers, and the annual fixed manufacturing costs in Table 5, Table 6 displays the PDV of the stream of fixed costs and its split for the periods 2020-2028 and 2007-2028. The PDV of DTCA spending in the U.S. from 2007-2019 is in the range of US$ 582 – 659 million (in 2018 US$), depending on the interest rate.

Table 6. PDV of the stream of fixed manufacturing and marketing costs from 2020-2028 and 2007-2028, in million 2018 US$, applying eq. (3).

Interest rate (*r*)	Estimate	PDV fixed manufact. costs, 2020-28	PDV marketing costs, 2020-28	Total 2020-2028	PDV fixed manufact. costs, 2007-28	PDV of marketing costs, 2007-28	Total 2007-2028
0.03	High	269.548	123.240	**392.788**	330.320	2,118.761	**2,449.082**
	Low	175.833	74.032	**249.865**	215.476	1,272.781	**1,488.257**
0.05	High	247.675	114.688	**362.363**	263.503	1,970.337	**2,233.840**
	Low	161.565	68.895	**230.460**	171.890	1,183.620	**1,355.509**
0.07	High	228.379	107.129	**335.508**	214.590	1,844.744	**2,059.335**
	Low	148.977	64.354	**213.332**	139.983	1,108.174	**1,248.156**

Source: Own calculations based on Table 5 and Table S11.

Assuming that global marketing spending on health providers is 50% and 150% of global DTCA spending for the “low” and “high” estimate, respectively, implies that the PDV of the stream of global marketing costs from the perspective of 2007 is in the range of US$ 1.11–2.12 billion (in 2018 US$). It exceeds the PDV of manufacturing fixed costs for the period 2007-2028 considerably (US$ 140–330 million) and is at least as high as R&D costs, as will become apparent in Section 3.4. We estimate that the PDV of future manufacturing costs from the perspective of 2020 amounts to US$ 149–270 million. It exceeds the PDV of the stream of marketing costs in the period 2020-2028 (based on the annual average in the period 2017-2019), reflecting that marketing spending has sharply declined some years after market introduction. The PDV of total future fixed costs from the perspective of 2020 is in the range of US$ 213–393 million. For the entire patent length, the PDV of the total fixed cost stream from the perspective of 2007 amounts to US$ 1.25–2.45 billion.

3.3 Estimated global value of Gardasil patents and the patent buyout price

Using eq. (4), Table 7 shows the patent value from 2007-2028 and for the remaining patent length, 2020-2028, based on the information the PDV of the stream of operating profits and fixed costs, respectively. The PDV of the future profit stream in Table 7 is somewhat lower than shown in Table 4 as we left out the PDV of the operating profit stream from GAVI supported countries. The reason is that these countries are not obliged to provide patent protection on vaccines until 2033 (64) such that a patent buyout is not beneficial. We include those profits to derive the total patent value for 2007-2028. We estimate the global patent buyout price in 2020 when assuming patent expiry in 2028 in the range of US$ 15.6–27.7 billion (in 2018 US$), whereas the total patent value from the perspective of 2007 amounts to US$ 17.8–42.8 billion (in 2018 US$).

Table 7. Estimated global patent buyout price in 2020 and total patent value of Gardasil (2007-2028) in million 2018 US$, applying eq. (4).

Interest rate (*r*)	Patent value estimate*	PDV of operating profits, 2020-28**	PDV of fixed costs, 2020-28	Global patent buyout price	PDV of operating profits, 2007-28	PDV of fixed costs, 2007-28	Total patent value
0.03	High	27,952.33	249.87	**27,702.46**	44,252.10	1’488.26	**42,763.84**
	Low	18,450.43	392.79	**18,057.64**	29,163.92	2’449.08	**26,714.84**
0.05	High	25,953.42	230.46	**25,722.96**	36,135.28	1’355.51	**34,779.77**
	Low	17,131.34	362.36	**16,768.97**	23,823.28	2’233.84	**21,589.44**
0.07	High	24,186.80	213.33	**23,973.46**	30,049.77	1’248.16	**28,801.62**
	Low	15,965.56	335.51	**15,630.06**	19,818.28	2’059.33	**17,758.94**

* For the high patent value estimate, we take the high estimate for the PDV of operating profits and deduct the low estimate of the PDV of fixed costs. Vice versa for the low patent value estimate. ** We did not include operating profits from GAVI supported countries.

Source: Own calculations based on Table S9 and Table 6.

3.4 R&D cost estimates for Gardasil and its relation to the patent value

We next relate the total value of the Gardasil patents in Table 7 to its R&D costs and discuss the result in view of the observed POS for finding new vaccines in the literature.

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 (84). The main aim of phase II is to demonstrate the efficacy and immunogenicity of the vaccine candidate in a larger group (84). 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 (61).

(15) 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 (in 2008 US$). Moreover, according to (20), the site costs are US$ 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 (average costs from 2004-2012 in current US$). We use these numbers jointly with the information of clinical trials (that includes subject numbers) to come up with R&D costs, separated by phases and type of cost.

Table 8. 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	94,070	376,279	18,372	73,488
	Total spent on sites	3,173,414	3,173,414	793,353	793,353
	Total spent of study costs	9,573,935	9,573,935	2,393,484	2,393,484
	Total spent on phase I clinical trials	12,841,419	13,123,628	3,202,637	3,250,037
Phase-II	Total spent on subjects	1,684,186	2,245,581	1,068,488	1,424,651
	Total spent on sites	22,042,500	22,042,500	17,634,000	17,634,000
	Total spent of study costs	36,472,581	36,472,581	29,178,065	29,178,065
	Total spent on phase II clinical trials	60,199,267	60,760,663	47,880,553	48,236,716
Phase-III	Total spent on subjects	107,539,535	161,309,302	77,297,674	115,946,512
	Total spent on sites	137,892,959	137,892,959	111,627,634	111,627,634
	Total spent of study costs	221,324,445	221,324,445	179,167,408	179,167,408
	Total spent on phase III clinical trials	466,756,940	520,526,707	368,092,716	406,741,553
	Total spent on clinical trials	539,797,626	594,410,998	419,178,479	458,238,595

Source: Own calculations based on Tables S12 and S13 jointly with Table S14a for Gardasil-4 and Table S14b for Gardasil-9.

As shown in Table 8, for Gardasil-4, we arrive at R&D costs in the range of US$ 539.80–594.41 million and for Gardasil-9 in the range of US$ 419.18–458.24 million.

Table 9 presents total R&D costs by adding up the documented outlays for Gardasil-4 and Gardasil-9 and R&D capital costs. Capital costs are assumed to be 10% and 15% of the low estimate and high estimate of the R&D costs presented in Table 8, respectively. Doing so, we estimate total R&D costs of both vaccines between US$ 1,054.9–1,210.5 million.

Table 9. 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*	95,897,610	157,897,439
Total Gardasil R&D costs	**1,054,873,715**	**1,210,547,032**

* 10% of Subtotal for the low estimate, 15% of the Subtotal for the high estimate.

Source: Own calculations based on Table 8.

We finally put our estimates for total R&D costs in relation to the estimates of the total value of the Gardasil patents. This provides us with a range for the innovation probability that is required to cover R&D costs in expected value of the patents, as defined by μ_0 in eq. (5). The lower bound is found by dividing the low estimate for R&D costs from Table 9 (US$ 1,055 million) and the high estimate of the patent value (US$ 42,764 million) from Table 7, which gives us μ_0 =0.025. For the upper bound, dividing the high estimate for R&D costs (US$ 1,210 million) and the low estimate of the patent value (US$ 17,759 million) implies μ_0 =0.068.

What do we know about the POS for vaccines targeting infectious diseases to which we can compare our estimate for μ_0? In a sample of more than 1,800 trials at phase I in the 2000s, (85) found a POS of about one third. In the previous literature, the lowest POS estimates from moving from phase I to phase II and from moving to phase II to phase III are 50% and 22%, respectively, whereas the highest POS estimates are 90% and 79%, respectively (86). This suggests a cumulative POS in clinical trials above 10%. Notably, the low POS estimates sometimes reported in the literature (87) include pre-clinical trials that are not applicable here. In sum, the POS estimates for other vaccines are significantly higher than our estimated μ_0, suggesting that the Gardasil patents generate extraordinarily high profits.

4. Concluding remarks

Patents are an effective strategy to prevent new entrants in the market. The high number of patent applications for HPV vaccines by Merck and GSK in emerging countries with a large pharmaceutical industry such as China, Brazil and India shows that it is a strategy commonly implemented (62). Patent buyouts for pharmaceuticals are potentially welfare-enhancing by removing monopoly price distortions and increasing drug availability by stimulating generic entry. Maintaining innovation incentives requires that the patent holder is fully compensated for its foregone profits. In this paper, we have calculated this patent buyout price for Merck's HPV vaccines as the PDV of the future profit stream until the patent expiry in 2028.

We estimated that the remaining patent buyout value for Gardasil supplied by Merck in 2020 as the PDV of the future stream of expected profits in the range of US$ 15.6–27.7 billion (in 2018 US$), depending on the assumed interest rate for discounting and the estimated ranges for the number of demanded doses, variable costs, and fixed costs. On the one hand, the estimated remaining private patent value may be viewed as an upper bound for the patent buyout price 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. On the other hand, given the private information of the patent holder, we may want propose a sufficiently high patent buyout price that is unlikely to fall short of the remaining patent value, to incentivize the patent holder to agree to the patent buyout. In sum, albeit calculating the net social benefit of the patent buyout is beyond the scope of this paper, the suggested range for the patent buyout price may be viewed as a benchmark for negotiating an agreement with the patent holder.

While the global patent buyout of Gardasil we suggest is incentive-compatible for the patent holder, it is a financially challenging proposal. A preferable albeit not necessarily successful strategy to reduce prices could be to reach a licensing agreement with Merck to allow generic manufacturing of Gardasil for LIC and MIC. The Medicines Patent Pool (MPP), a United Nations-backed global health organization, negotiates with pharmaceutical companies and other global health stakeholders (i.e. governments and NGOs) licensing to allow generic companies to manufacture low cost medicines for LIC and MIC (88). This patent pooling model has been successfully implemented for medicines against tuberculosis, HIV and hepatitis: 13 HIV antiretrovirals, three Hepatitis C direct-acting antivirals and one tuberculosis treatment have been licensed through MPP (88). Merck licensed Raltegravir through MPP, a pediatric HIV antiretroviral medicine, for generic production for LIC and MIC (89). However, this licensing agreement does not cover technology and data owned by Merck and in the case of Gardasil such an agreement has not been reached yet. The main obstacle to the MPP solution could be the concern of patent holders that entry of generic manufacturers may affect the market in HIC by parallel imports or a public debate on prices charged by the original manufacturer.

In order to assess the price setting power of Merck in providing its HPV vaccines, we have also estimated both the R&D costs and the global patent value, which is the PDV of the profit stream for the period 2007-2028. The ratio of these figures is the POS needed to break even in expected value. Using information on clinical trials, we estimated the R&D costs for the Gardasil innovation to be around US$ 1.05–1.21 billion, while the global patent value amounts to US$ 17.8–42.8 billion. The implied R&D to patent value ratio of 2.5–6.8% is below the average POS in clinical trials for vaccines found in the literature. As a caveat and suggestion for future research, making the point that the current patent system generates excessive price setting power, i.e. is more generous than needed to elicit desirable R&D effort, would require estimations of the relationship between R&D cost and the patent value for many more pharmaceuticals.

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Supporting Information

Throughout the paper, we converted all monetary variable values to 2018 US$, according to Table S0.

Table S0. Consumer price index (CPI) with base year 2015 and price index (PI) with base year 2018.

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

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

Source: Federal Reserve Bank (71) and own calculations.

To derive operating profits using eq. (1), we need prices, number of sold units, and variable costs.

Table S1. Prices of Gardasil-4 and Gardasil-9 outside the U.S. in year 2016.*

	2016, in current 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	n.a.	20.52	n.a.
GAVI	4.50	n.a.	4.69	n.a.
India	6.90	n.a.	7.19	n.a.
Indonesia	14.76	n.a.	15.38	n.a.
China	120.00	153.00	125.00	159.38

* Median prices for middle-income countries (MIC) and high-income countries (HIC). ** Deflated prices using the price index for 2016, PI=0.956 (Table S0). n.a.: Not applicable because Gardasil-9 has not been sold in these regions.

Sources: HIC, MIC (includes purchases mediated by PAHO), GAVI (9); India (77); Indonesia (78); China (75,76) and own calculations.

Table S2. 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$)***	Estimated Price (in 2018 US$)****
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

* Prices for Gardasil-4 in 2007-2015 and for Gardasil-9 for 2016-2018. **CDC refers to prices for sales mediated by Centers for Disease Control (CDC) funded programs. *** Simple average of numbers in columns 2 and 3. **** Deflated by the PI as given in Table S0.

Source: CDC (42) and own calculations.

GAVI (2017) gives estimates on the number of units for 2010-2017 and predictions for 2018-2027 for HIC as a whole and for other regions. The number of units is thus not readily available as breakdown of HIC numbers into those sold in the U.S. and those sold in other HIC. We also do not have estimates for the period 2007-2009. We can derive, however, the market share for the period 2015-2017 in the U.S. and know that in period 2007-2009 Gardasil has only been sold in HIC. Using revenue information in Table 1 of the main text, the missing data to generate the middle estimates for 2007-2017 in Table 2 ("Number of Gardasil doses sold in different countries and country groups…") is derived accordingly in Tables S3a-S3c.

Table S3a. U.S. market share, 2015-2017.

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

Source: Merck (79).

Table S3b. 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$)				
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 S3a, using total revenues from Table 1 (main text). ** The column restates the average median price in the U.S. from Table S2, assuming that 50% of sales are mediated by CDC funded programs.

Sources: GAVI (18) and own calculations.

Table S3c. 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

* Revenue information for non-U.S. countries from Table S3b (these are HIC in 2007-2009). ** Prices from Table S1 deflated by PI from Table S0. *** Revenue in column 2 divided by price in column 3.

For the forecasts (2018-2027) in Table 2 of the main text we employ the average U.S. market share in period 2010-2017 as derived in Table S4 for the breakdown of the number of units sold in the U.S. vs. other HIC.

Table S4. 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. sales 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. sales share 2010-2017 (in %)			**59.8**

* Calculated in Table S3b.

Source: GAVI (18) and own calculations.

Table S5a and Table S5b summarize the derived middle estimates of the number of doses for the periods 2007-2017 and 2018-2027 (forecasts), respectively: they also display the "high" estimates (adding 20% to the middle estimate) and the "low" estimates (subtracting 20% from the middle estimate) that account for uncertainty in the estimates and predictions. The "high" and "low" estimates by region enter the calculations of operating profits (Table S9). From those, we can derive the PDV of operating profits for the two scenarios as given in Table 4 of the main text by applying eq. (2).

Table S5a. Number of Gardasil doses in different regions in millions, 2007-2017, different scenarios.

Year	Estimate	Number of doses (in millions)							
		HIC total	U.S.*	Other HIC**	MIC	GAVI	India/ Indonesia	China	Total
2007	Low (-20%)	15.68	8.34	7.34	0	0	0	0	15.68
	Middle	19.60	10.42	9.18	0	0	0	0	19.60
	High (+20%)	23.52	12.50	11.02	0	0	0	0	23.52
2008	Low (-20%)	14.30	7.60	6.70	0	0	0	0	14.30
	Middle	17.88	9.50	8.38	0	0	0	0	17.88
	High (+20%)	21.46	11.40	10.06	0	0	0	0	21.46
2009	Low (-20%)	11.16	5.80	5.36	0	0	0	0	11.16
	Middle	13.95	7.25	6.70	0	0	0	0	13.95
	High (+20%)	16.74	8.70	8.04	0	0	0	0	16.74
2010	Low (-20%)	12.53	5.06	7.47	4.87	0	0	0	17.40
	Middle	15.66	6.32	9.34	6.09	0	0	0	21.75
	High (+20%)	18.79	7.59	11.21	7.31	0	0	0	26.10
2011	Low (-20%)	16.70	6.54	10.16	9.05	0	0	0	25.75
	Middle	20.88	8.18	12.70	11.31	0	0	0	32.19
	High (+20%)	25.06	9.82	15.24	13.57	0	0	0	38.63
2012	Low (-20%)	14.62	8.53	6.09	11.14	0	0	0	25.75
	Middle	18.27	10.66	7.61	13.92	0	0	0	32.19
	High (+20%)	21.92	12.79	9.14	16.70	0	0	0	38.63
2013	Low (-20%)	13.92	9.23	4.69	11.14	0.70	0	0	25.75
	Middle	17.40	11.54	5.86	13.92	0.87	0	0	32.19
	High (+20%)	20.88	13.85	7.03	16.70	1.04	0	0	38.63
2014	Low (-20%)	12.18	8.10	4.08	9.05	0.70	0	0	21.92
	Middle	15.23	10.13	5.10	11.31	0.87	0	0	27.41
	High (+20%)	18.27	12.15	6.12	13.57	1.04	0	0	32.89
2015	Low (-20%)	11.83	8.65	3.18	7.66	1.39	0	0	20.88
	Middle	14.79	10.81	3.98	9.57	1.74	0	0	26.10
	High (+20%)	17.75	12.97	4.78	11.48	2.09	0	0	31.32
2016	Low (-20%)	12.53	9.11	3.42	7.66	2.09	0.70	0	22.97
	Middle	15.66	11.39	4.27	9.57	2.61	0.87	0	28.71
	High (+20%)	18.79	13.66	5.13	11.48	3.13	1.04	0	34.45
2017	Low (-20%)	12.53	7.80	4.73	7.66	1.39	0.70	0	22.27
	Middle	15.66	9.75	5.91	9.57	1.74	0.87	0	27.84
	High (+20%)	18.79	11.70	7.09	11.48	2.09	1.04	0	33.41
Total	**Low (-20%)**	106.84	**63.02**	**43.82**	**68.21**	**6.26**	**1.39**	**0**	**182.70**
	Middle	133.55	**78.77**	**54.77**	**85.26**	**7.83**	**1.74**	**0**	**228.38**
	High (+20%)	160.25	**94.53**	**65.73**	**102.31**	**9.40**	**2.09**	**0**	**274.05**

* For the U.S. middle estimates, see Table S3b. ** Implied by subtracting U.S. numbers from HIC total.

Table S5b. Number of Gardasil doses in different regions in millions, 2018-2027, different scenarios.

Year	Estimate	Number of doses (in millions)							
		HIC total	U.S.*	Other HIC**	MIC	GAVI	India/ Indonesia	China	Total
2018	Low (-20%)	11.83	7.08	4.76	8.35	4.18	0.70	0	25.06
	Middle	14.79	8.84	5.95	10.44	5.22	0.87	0	31.32
	High (+20%)	17.75	10.61	7.13	12.53	6.26	1.04	0	37.58
2019	Low (-20%)	12.18	7.28	4.90	9.74	18.79	0.70	0	41.41
	Middle	15.23	9.10	6.12	12.18	23.49	0.87	0	51.77
	High (+20%)	18.27	10.93	7.34	14.62	28.19	1.04	0	62.12
2020	Low (-20%)	13.22	7.91	5.32	10.44	27.84	0.70	0	52.20
	Middle	16.53	9.88	6.65	13.05	34.80	0.87	0	65.25
	High (+20%)	19.84	11.86	7.97	15.66	41.76	1.04	0	78.30
2021	Low (-20%)	12.53	7.49	5.04	10.44	21.58	11.14	0	55.68
	Middle	15.66	9.36	6.30	13.05	26.97	13.92	0	69.60
	High (+20%)	18.79	11.24	7.55	15.66	32.36	16.70	0	83.52
2022	Low (-20%)	11.83	7.08	4.76	10.44	22.97	20.18	0.70	66.12
	Middle	14.79	8.84	5.95	13.05	28.71	25.23	0.87	82.65
	High (+20%)	17.75	10.61	7.13	15.66	34.45	30.28	1.04	99.18
2023	Low (-20%)	11.14	6.66	4.48	10.44	25.06	18.79	2.09	67.51
	Middle	13.92	8.32	5.60	13.05	31.32	23.49	2.61	84.39
	High (+20%)	16.70	9.99	6.72	15.66	37.58	28.19	3.13	101.27
2024	Low (-20%)	10.44	6.24	4.20	11.14	17.40	19.49	2.78	61.25
	Middle	13.05	7.80	5.25	13.92	21.75	24.36	3.48	76.56
	High (+20%)	15.66	9.36	6.30	16.70	26.10	29.23	4.18	91.87
2025	Low (-20%)	9.74	5.83	3.92	11.83	22.27	17.40	2.78	64.03
	Middle	12.18	7.28	4.90	14.79	27.84	21.75	3.48	80.04
	High (+20%)	14.62	8.74	5.88	17.75	33.41	26.10	4.18	96.05
2026	Low (-20%)	9.74	5.83	3.92	11.83	20.88	16.01	3.48	61.94
	Middle	12.18	7.28	4.90	14.79	26.10	20.01	4.35	77.43
	High (+20%)	14.62	8.74	5.88	17.75	31.32	24.01	5.22	92.92
2027	Low (-20%)	9.74	5.83	3.92	11.83	20.18	14.62	4.87	61.25
	Middle	12.18	7.28	4.90	14.79	25.23	18.27	6.09	76.56
	High (+20%)	14.62	8.74	5.88	17.75	30.28	21.92	7.31	91.87
Total	**Low (-20%)**	112.40	**67.22**	**45.19**	**106.49**	**201.14**	**119.71**	**16.70**	**556.45**
	Middle	140.51	**84.02**	**56.48**	**133.11**	**251.43**	**149.64**	**20.88**	**695.57**
	High (+20%)	168.61	**100.83**	**67.78**	**159.73**	**301.72**	**179.57**	**25.06**	**834.68**

* Assuming for the middle estimates that number doses sold in the U.S. corresponds to 59.8% of total number of doses sold in HIC markets (see Table S4). ** Implied by subtracting U.S. numbers from HIC total.

Source: GAVI (18) and own calculations.

We next come to variable costs that are composed of capital costs, costs for materials, costs for filling and packaging, and labor costs. Based on variable costs, the price information presented in Tables S1 and S2, and the number of units in Tables S5a and S5b, we can apply eq. (1) to compute operating profits, and accordingly eq. (2) to compute the PDV of the stream of operating profits.

We first restate in Table S6a the calculation of Clendinen *et al.* (12) who annualize capital costs by assuming a 5% real (no inflation) discount rate and a useful life of 10 years for equipment and 25 years for building. The range of costs reflects uncertainty in estimates. In Table S6b we obtain variable capital costs by dividing the total annualized capital costs by the average number of doses per year produced in the period 2010-2017, using the middle estimates in Table 5a.

Table S6a. Total investment costs and annualized capital costs for Gardasil-4, in million 2014 US$.

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

Source: Clendinen *et al.* (12).

Table S6b. Estimated variable capital costs (per year) for manufacturing one million doses of Gardasil-4**.**

	Low estimate	**High estimate**
Variable building cost (annualized capital cost/28.55 million)*	238,204.71	395,840.18
Variable equipment cost (annualized capital cost/28.55 million)*	217,186.64	360,810.07
Total variable capital cost for one million doses (in 2014 US$)	455,391.35	756,650.25
Total variable capital cost for one million doses (in 2018 US$)**	428,067.87	711,251.24

* To obtain variable costs per million doses, variable capital costs from Table S6a are divided by the average number of doses sold per year between 2010-2017 (i.e. 228.38/8=28.55 million, according to middle estimates in Table S5a). ** Numbers in row 3 deflated by price index for 2014, PI=0.942 (Table S0).

Source: Own calculations.

Costs for materials are derived in Table S7, whereas Table S8 presents the estimates of variable labor costs. Table 3 of the main text shows total variable costs based on Tables S6b-S8.

Table S7. Estimated cost of materials for producing one million doses of Gardasil-4.

Materials (units)	Units per package sold by life science companies	Price per package (2013 US$)	Number of units needed per million doses	Price for one million doses (2013 US$)*
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**

* The price for one million doses in the last column 4 is obtained by multiplying the numbers in column 2 and 3 and dividing by the units per package in column 1 ** Deflated by price index for 2013, PI=0.928 (Table S0).

Source: Clendinen *et al.* (12) and own calculations.

According to Clendinen *et al.* (12), 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. Based on their estimates, we arrive at Table S8 for variable labor costs.

Table S8. Variable labor cost for producing one million doses of Gardasil-4.

Number of employees	Personnel	Salary costs per employee for one million doses (in 2014 US$)		Variable labor costs (in 2014 US$) 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

* Total variable costs deflated by the price index for 2014, PI=0.942 (Table S0).

Source: Clendinen *et al.* (12) and own calculations.

Table S9 uses prices, number of units, and variable costs to calculate operating profits.

Table S9. Detailed calculation for Table 4 of operating profits for different countries and country groups (a) 2007-2009, (b) 2010-2019 and (c) 2019-2028, applying eq. (1).

a) Operating profits estimation, 2007-2009

			2007	**2008**	**2009**
U.S.	Price		131.55	131.72	138.03
	Variable costs	Low	1.00	1.00	1.00
		High	1.59	1.59	1.59
	# doses (in millions)	Low	8.34	7.60	5.80
		High	12.50	11.40	8.70
	Profit (in million 2018 US$)	Low	1,083.37	989.00	791.33
		High	1,632.43	1,490.23	1,192.13
Other HIC	Price		45.96	45.96	45.96
	Variable costs	Low	1.00	1.00	1.00
		High	1.59	1.59	1.59
	# doses (in millions)	Low	7.34	6.70	5.36
		High	11.02	10.06	8.04
	Profit (in million 2018 US$)	Low	325.84	297.45	237.81
		High	495.26	452.10	361.47
Total profit (in million 2018 US$)		**Low**	**1,409.21**	**1,286.45**	**1,029.15**
		High	**2,127.69**	**1,942.33**	**1,553.59**

b) Operating profits estimation, 2010-2019

			2010	2011	2012	2013	2014	2015	2016	2017	2018	2019
U.S.	Price		137.61	126.16	127.99	130.76	139.17	148.96	163.57	164.47	180.64	180.64
	Variable costs	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
	# doses (in millions)	Low	5.06	6.54	8.53	9.23	8.10	8.65	9.11	7.80	7.08	7.28
		High	7.59	9.82	12.79	13.85	12.15	12.97	13.66	11.70	10.61	10.93
	Profit (in million 2018 US$)	Low	687.90	815.15	1,077.57	1,192.56	1,114.75	1,274.54	1,475.37	1,270.18	1,266.87	1,304.14
		High	1,036.33	1,228.51	1,623.91	1,797.02	1,679.30	1,919.46	2,221.12	1,912.17	1,906.57	1,962.65
Other HIC	Price		45.96	45.96	45.96	45.96	45.96	45.96	45.96	45.96	45.96	94.79
	Variable costs	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# doses (in millions)	Low	7.47	10.16	6.09	4.69	4.08	3.18	3.42	4.73	4.76	4.90
		High	11.21	15.24	9.14	7.03	6.12	4.78	5.13	7.09	7.13	7.34
	Profit (in million 2018 US$)	Low	331.46	450.79	270.24	207.96	180.91	141.24	151.71	209.84	211.04	456.34
		High	503.80	685.17	410.75	316.09	274.97	214.68	230.59	318.95	320.76	688.84
MIC	Price		20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52
	Variable costs	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
	# doses (in millions)	Low	4.87	9.05	11.14	11.14	9.05	7.66	7.66	7.66	8.35	9.74
		High	7.31	13.57	16.70	16.70	13.57	11.48	11.48	11.48	12.53	14.62
	Profit (in million 2018 US$)	Low	92.23	171.29	210.81	210.81	171.29	144.93	144.93	144.93	158.11	184.46
		High	142.66	264.94	326.08	326.08	264.94	224.18	224.18	224.18	244.56	285.32
GAVI	Price					4.69	4.69	4.69	4.69	4.69	4.69	4.69
	Variable costs	Low				1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High				1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# doses (in millions)	Low	0.00	0.00	0.00	0.70	0.70	1.39	2.09	1.39	4.18	18.79
		High	0.00	0.00	0.00	1.04	1.04	2.09	3.13	2.09	6.26	28.19
	Profit (in million 2018 US$)	Low	0.00	0.00	0.00	2.16	2.16	4.31	6.47	4.31	12.94	58.21
		High	0.00	0.00	0.00	3.85	3.85	7.70	11.55	7.70	23.10	103.94
Indonesia and India	Price								11.28	11.28	11.28	11.28
	Variable costs	Low							1.00	1.00	1.00	1.00
		High							1.59	1.59	1.59	1.59
	# doses (in millions)	Low	0.00	0.00	0.00	0.00	0.00	0.00	0.70	0.70	0.70	0.70
		High	0.00	0.00	0.00	0.00	0.00	0.00	1.04	1.04	1.04	1.04
	Profit (in million 2018 US$)	Low	0.00	0.00	0.00	0.00	0.00	0.00	6.75	6.75	6.75	6.75
		High	0.00	0.00	0.00	0.00	0.00	0.00	10.73	10.73	10.73	10.73
Total profit (in million 2018 US$)		**Low**	**1,111.59**	**1,437.22**	**1,558.63**	**1,613.49**	**1,469.10**	**1,565.02**	**1,785.23**	**1,636.02**	**1,655.70**	**2,009.89**
		High	**1,682.79**	**2,178.62**	**2,360.74**	**2,443.03**	**2,223.05**	**2,366.01**	**2,698.17**	**2,473.73**	**2,505.73**	**3,051.49**

c) Operating profit estimation, 2020-2028

			2020	**2021**	**2022**	**2023**	**2024**	**2025**	**2026**	**2027/2028**
U.S.	Price		180.64	180.64	180.64	180.64	180.64	180.64	180.64	180.64
	Variable costs	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
	# doses (in millions)	Low	7.91	7.49	7.08	6.66	6.24	5.83	5.83	5.83
		High	11.86	11.24	10.61	9.99	9.36	8.74	8.74	8.74
	Profit (in million 2018 US$)	Low	1,415.92	1,341.40	1,266.87	1,192.35	1,117.83	1,043.31	1,043.31	1,043.31
		High	2,130.88	2,018.73	1,906.57	1,794.42	1,682.27	1,570.12	1,570.12	1,570.12
Other HIC	Price		94.79	94.79	94.79	94.79	94.79	94.79	94.79	94.79
	Variable costs	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# doses (in millions)	Low	5.32	5.04	4.76	4.48	4.20	3.92	3.92	3.92
		High	7.97	7.55	7.13	6.72	6.30	5.88	5.88	5.88
	Profit (in million 2018 US$)	Low	495.46	469.38	443.30	417.23	391.15	365.07	365.07	365.07
		High	747.89	708.53	669.16	629.80	590.44	551.08	551.08	551.08
MIC	Price		20.52	20.52	20.52	20.52	20.52	20.52	20.52	20.52
	Variable costs	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
	# doses (in millions)	Low	10.44	10.44	10.44	10.44	11.14	11.83	11.83	11.83
		High	15.66	15.66	15.66	15.66	16.70	17.75	17.75	17.75
	Profit (in million 2018 US$)	Low	197.64	197.64	197.64	197.64	210.81	223.99	223.99	223.99
		High	305.70	305.70	305.70	305.70	326.08	346.46	346.46	346.46
GAVI	Price		4.69	4.69	4.69	4.69	4.69	4.69	4.69	4.69
	Variable costs	Low	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
		High	1.59	1.59	1.59	1.59	1.59	1.59	1.59	1.59
	# doses (in millions)	Low	27.84	21.58	22.97	25.06	17.40	22.27	20.88	20.18
		High	41.76	32.36	34.45	37.58	26.10	33.41	31.32	30.28
	Profit (in million US$)	Low	86.23	66.83	71.14	77.61	53.90	68.99	64.68	62.52
		High	153.99	119.34	127.04	138.59	96.24	123.19	115.49	111.64
Indonesia and India	Price		11.28	11.28	11.28	11.28	11.28	11.28	11.28	11.28
	Variable costs	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
	# doses (in millions)	Low	0.70	11.14	20.18	18.79	19.49	17.40	16.01	14.62
		High	1.04	16.70	30.28	28.19	29.23	26.10	24.01	21.92
	Profit (in million 2018 US$)	Low	6.75	107.92	195.61	182.12	188.86	168.63	155.14	141.65
		High	10.73	171.74	311.28	289.81	300.54	268.34	246.87	225.41
China	Price				159.38	159.38	159.38	159.38	159.38	159.38
	Variable costs	Low			1.00	1.00	1.00	1.00	1.00	1.00
		High			1.59	1.59	1.59	1.59	1.59	1.59
	# doses (in millions)	Low	0.00	0.00	0.70	2.09	2.78	2.78	3.48	4.87
		High	0.00	0.00	1.04	3.13	4.18	4.18	5.22	7.31
	Profit (in million 2018 US$)	Low	0.00	0.00	109.82	329.46	439.27	439.27	549.09	768.73
		High	0.00	0.00	165.34	496.03	661.37	661.37	826.72	1,157.40
Total profit (in million 2018 US$)		**Low**	**2,201.99**	**2,183.17**	**2,284.38**	**2,396.40**	**2,401.83**	**2,309.26**	**2,401.28**	**2,605.27**
		High	**3,349.18**	**3,324.03**	**3,485.09**	**3,654.35**	**3,656.94**	**3,520.56**	**3,656.73**	**3,962.10**

Source: Own calculations based on Tables S1, S2, S5a, S5b and Table 3.

We next present the details for the estimation of fixed manufacturing costs that are displayed in Table 5. Table S10a starts with the derivation of annual fixed labor compensation, based on hourly compensation and the required number of directors, managers and supervisors per factory as provided by Clendinen *et al.* (12). Factory and administrative overhead (in 2018 US$) costs are computed in Table S10b, assumed to be 45% of the sum of total labor costs plus the costs for materials. From 2022 onwards, the total fixed manufacturing cost is based on three factories rather than one. The assumptions are discussed in Section 2.3 (main text).

Table S10a. Annual manufacturing fixed costs, in 2014 US$ – detailed derivation of Table 5.

	Personnel	**Annual Compensation**		**Total Costs**	
Fixed number of employees per factory	**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
Fixed costs for indicated personnel (in 2014 US$)				940,000.00	1,350,000.00
Fixed costs for indicated personnel (in 2018 US$)**				**1,000,000.00**	**1,436,170.21**
Factory and administrative overhead (in 2018 US$)*				**7,740,365.58**	**11,962,632.65**
Total fixed costs per factory per year (in 2018 US$) (2007-2021)				**8,740,365.58**	**13,398,802.86**
Total fixed costs in 3 factories per year (from 2022)				**26,221,096.74**	**40,196,408.58**

* Derived in Table S10b. ** Deflated by price index for 2014, PI=0.942 (Table S0).

Source: Clendinen *et al.* (12) and own calculations.

Table S10b. Low and high estimate for the factory and administrative overhead, in 2018 US$.

		Low estimate	**High estimate**
Annual personnel cost	**Fixed***	1,000,000	1,436,170
	Variable (cost of 1 million x 28.55)**	6,952,110	9,732,955
Cost of materials (cost of 1 million x 28.55)**		9,248,702	15,414,503
Total		17,200,812	26,583,628
Annual factory and administrative overhead costs (45% costs of personnel and material)		7,740,366	11,962,633

* Manufacturing fixed costs are taken from Table S10a. ** For variable costs of labor and materials per one million doses, see Table 3. These are multiplied by the average number of doses sold per year between 2010-2017 (i.e. 228.38/8=28.55 million, according to Table S3b).

Source: Clendinen *et al.* (12) and own calculations.

The information from Table S10a is taken over in the left panel of Table S11 to summarize manufacturing fixed costs. The right panel of Table S11 presents the sum of DTCA spending in the U.S (90% of global DTCA spending) and the estimates for marketing expenditure on health providers (150% and 50% of global DTCA spending for the "high estimate" and "low" estimate, respectively); see Section 2.3. The information in Table S11 is used by applying eq. (3) to compute the PDV of the stream of fixed manufacturing and marketing costs from 2020-2028 and 2007-2028. Results are presented in Table 6 of the main text.

Table S11. Estimated fixed manufacturing and marketing costs from 2007-2028, in million 2018 US$.

	Manufacturing fixed costs*		**Marketing costs****	
	High estimate	**Low estimate**	**High estimate**	**Low estimate**
2007	13.399	8.740	502.81**	302.05**
2008	13.399	8.740	334.05	200.67
2009	13.399	8.740	218.30	131.14
2010	13.399	8.740	168.83	101.42
2011	13.399	8.740	134.58	80.85
2012	13.399	8.740	137.81	82.79
2013	13.399	8.740	152.27	91.47
2014	13.399	8.740	211.06	126.79
2015	13.399	8.740	213.92	128.51
2016	13.399	8.740	140.27	84.27
2017	13.399	8.740	8.89	5.34
2018	13.399	8.740	36.02	21.64
2019	13.399	8.740	1.20	0.72
2020	13.399	8.740	15.37	9.23
2021	13.399	8.740	15.37	9.23
2022-2028	40.196	26.221	15.37	9.23

* From Table S10a. ** We assume that marketing spending on health providers is 50% ("low" scenario) and 150% ("high" scenario) of the direct to consumer advertising (DTCA) spending, respectively, and that 90% of the marketing spending is in the U.S. Moreover, marketing costs in 2007 (the first full year Gardasil was sold) include costs of 2006 and the annual marketing costs for the period 2020-2028 equals the average of the annual marketing costs from 2017-2019. DTCA spending originally in current Euro. All numbers converted to current US$ using the exchange rate from Thomson Reuters and then deflated by PI from Table S0.

Source: Clendinen *et al.* (12), 'The Nielsen Company' (DTCA spending for the U.S.), and own calculations.

We calculate R&D costs for each phase as given in Table 8 as follows. We use the bounds of the cost range per subject provided by Light *et al.* (15) as given in Table S12 and multiply them by the number of subjects as given in Table S14a for Gardasil-4 and S14b for Gardasil-9. Analogously, we use the site cost and study cost estimates by Sertkaya *et al.* (20) given in Table S13 jointly with Tables S14a and S14b. As Sertkaya *et al.* (20) originally provide average costs from 2004-2012 in current US$, we use the price index PI in Table S0 for the median year 2008 to calculate corresponding costs in 2018 US$.

Table S12. 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=0.86 for year 2008 (Table S0).

Source: Light *et al.* (15).

Table S13. 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 (Table S0).

Source: Sertkaya *et al.* (20).

Table S14a. Estimated costs of R&D from phase I to phase III clinical trial for Gardasil-4, in 2018 US$.

Phase	#	Description	# of subjs	Costs estimation per subject*		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: (90)	249	116	465	28,953	115,814
	2***	• 40 women, aged 16-23 years, were randomly assigned (2:1 vaccine to placebo ratio) to receive either HPV18 L1 VLP vaccine or placebo. •Source: (91)	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: (92)	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 S12. ** From estimates displayed in Table S13. *** 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 S14b. Estimated costs of R&D from phase I to phase III clinical trial for Gardasil-9, in 2018 US$.

Phase	#	Description	# of subjs	Costs estimation per subject*		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 • Duration: September 2017 - November 2018 • ID: NCT03158220	1212	2,326	3,488	2,818,605	4,227,907

	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**	**458,238,595**

* From estimates displayed in Table S12. ** From estimates displayed in Table S13.