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Manufacturing costs of HPV vaccines for developing countries

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ABSTRACT

Background: Nearly all of the 500,000 new cases of cervical cancer and 270,000 deaths occur in middle or lower-income countries. Yet the two most prevalent HPV vaccines are unaffordable to most. Even prices to Gavi, the Vaccine Alliance, are unaffordable to graduating countries, once they lose Gavi subsidies. Merck and GlaxoSmithKline (GSK) claim their prices to Gavi equal their manufacturing costs; but these costs remain undisclosed. We undertook this investigation to estimate those costs.

Methods: Searches in published and commercial literature for information about the manufacturing of these vaccines. Interviews with experts in vaccine manufacturing.

Findings: This detailed sensitivity analysis, based on the best available evidence, finds that after a first set of batches for affluent markets, manufacturing costs of Gardasil for developing countries range between $0.48 and $0.59 a dose, a fraction of its alleged costs of $4.50. Because volume of Cervarix is low, its per unit costs are much higher, though at comparable volumes, its costs would be similar.

Interpretation: Given the recovery of fixed and annual costs from sales in affluent markets, Merck’s break-even price to Gavi could be $0.50–$0.60, not $4.50. These savings could support Gavi programs to strengthen delivery and increase coverage. Outside Gavi, prices to lower- and middle-income countries, with profit, could also be lowered and made available to millions more adolescents at risk. These estimates and their policy implications deserve further discussion.

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1. Introduction

Cervical cancer is the second most common cancer in females, with over 500,000 new cases per year worldwide. Approximately 85% of these new cases and over 90% of the 270,000 deaths from cervical cancer occur in lower- and middle-income countries, where cervical cancer remains a leading cause of death [1,2]. Human papillomavirus (HPV) infection is linked to >99% of cervical cancers [3]. While infection with most strains of HPV are transient and benign, 16 HPV strains are linked to cancerous and precancerous lesions in the genital and oral areas [4,5]. HPV-16 and -18 are associated with 70% of invasive cervical cancers worldwide, as well as cancer of the vulva, vagina, anus, and throat [6,7].

Two vaccines were developed to prevent HPV-16/18 related cancers. The quadrivalent HPV recombinant vaccine called Gardasil-4 and the bivalent HPV vaccine called Cervarix were developed by Merck and GlaxoSmithKline (GSK) respectively. Although Merck has subsequently developed Gardasil-9, Gardasil-4 and Cervarix remain widely used and are supplied by contract to Gavi, the Vaccine Alliance (Gavi), a public private partnership that provides financial subsidies to accelerate the introduction of new and under-utilized vaccines in the poorest countries of the world.

Gardasil-4 consists of four virus-like particles derived from HPV types 6, 11, 16 and 18. Cervarix consists of two virus-like particles derived from HPV types 16 and 18. When administered before sexual activity, these vaccines are 99 percent effective in preventing associated cancers [8]. Gardasil-4 also protects against genital warts associated with HPV-6 and -11 [9] and may induce cross-protection against oncogenic serotypes HPV-31 and -45 [10]. In 2009, the World Health Organization (WHO) recommended both HPV vaccines for girls aged 9–13, which Gavi promptly adopted [11]. As of 2015, WHO now recommends two doses of these vaccines, spaced 6–12 months apart, for girls aged 9–13 [12]. As the first vaccines against HPV-related cancers, the retail prices for Gardasil-4 and Cervarix were high, at US$150–$190 per dose. Negotiated prices to third parties are usually undisclosed. The lowest known prices outside Gavi are US$12.83 for Gardasil-4 and $0.50–$0.60 for Cervarix. Prices to Gavi, the Vaccine Alliance, are unaffordable to graduating countries, once they lose Gavi subsidies. Merck and GlaxoSmithKline (GSK) claim their prices to Gavi equal their manufacturing costs; but these costs remain undisclosed. We undertook this investigation to estimate those costs.

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in Brazil and $12.87 for Cervarix in South Africa [2]. Although these vaccines have been licensed in over 100 countries, several factors have contributed to low uptake [13–15]. Chief among these factors is the price of the vaccines [14].

In 2013, Merck offered to sell Gardasil to Gavi for US$4.50, and the President of Merck Vaccines said, “The price is what we calculate to be our cost of goods. As we expand volumes, the cost per unit can go down. Our intent is to sell it to Gavi at a price that does not bring profit to Merck.” She made it clear that manufacturing costs do not include research and other costs. [16]. GSK made similar statements and offered Cervarix for $4.60 a dose. Since neither manufacturer provided evidence of its cost of goods, this study was undertaken to determine what they are and how they vary by volume. Determining these closely held costs is difficult, and few detailed studies have been published [17]. This study presents the first detailed cost estimate of the complex manufacturing process of new-generation vaccines Gardasil-4 and Cervarix. It provides important insights into global price barriers and a useful framework for research and decisions concerning accessible pricing. Its limitations underscore the need for greater transparency in vaccine pricing.

2. Methods

We searched the published, grey, commercial, and company literature for information pertinent to the manufacturing and costs of these vaccines. We used Scopus, Web of Science, PubMed, Proquest, Factiva and Bloomberg, using various combinations of these search terms: vaccine, production, manufacturing, cost, and costs. Company reports and past press releases were also helpful. We also identified experts in manufacturing through our contacts and authors of pertinent reports, talks or articles. We gained insights from corresponding and interviewing some of them. Costs fall into four categories: fixed annualized capital costs of building, pipes, equipment, and Good Manufacturing Practices (GMP) specifications; two kinds of variable costs, annual costs for labor and per-batch costs for raw materials and filling and packaging the vials; and factory overheads (indirect costs). In accordance with standard accounting practices for estimating costs of manufacturing, other costs are not included such as research and development (R&D), marketing, or general administration and legal services [17–19]. In particular, R&D to discover and develop a drug or vaccine are widely regarded as sunk costs and not part of manufacturing costs, as the President of Merck Vaccines, experts cited here, and the UNIDO Manual over its many editions state [20]. R&D costs after a product is approved reflect investment decisions on using profits from sales to improve, upgrade, extend, or expand on that product for further sales. Brief summaries of the major categories of expense are given here. See Appendix A (details on manufacturing cost estimates) for further details.

2.1. Annualized capital costs

Annualized capital costs estimate the cost of replacing manufacturing facilities, which include buildings, pipes, equipment, lines and GMP (Good Manufacturing Practices) up to beginning production. Following accepted accounting and economic evaluation practices [17,18], equipment constitutes about one-third of total cost. Annualized capital costs assume a 5% real (no inflation) discount rate, 10 years of useful life for the equipment, and 25 years of useful life for the building [17].

For sensitivity analysis, as described in Appendix A, capital costs were estimated based on the share of the total manufacturing complex used for Gardasil or Cervarix, at most one quarter of the total complex cost. For Gardasil, one quarter of the $1 billion spent by Merck in building its manufacturing complex in Durham, NC was used as the high estimate; a 20% discount, or $200 million for the middle estimate; and a 40% discount, or $150 million for the low estimate. For Cervarix, one quarter of the $830 million spent by GSK in building its manufacturing complex in France was used as the high estimate; a 20% discount, or $166 million for the middle estimate; and a 40% discount, or $124.5 million for the low estimate. Thus the low, middle, and high annualized capital costs to replace all buildings and equipment associated with manufacturing Gardasil-4 are $12.9 million, $17.2 million, and $21.5 million respectively. The low, middle, and high annualized capital costs for manufacturing Cervarix are $10.7 million, $14.3 million, and $17.9 million respectively.

2.2. Vaccine yield

The number of doses that can be made from a given batch produced with the raw materials and equipment critically affects cost. As explained in Appendix A, the yield for Gardasil-4 is estimated to be 29 mg/L, and for Cervarix 40 mg/L. The Gardasil-4 vaccine consists of a 0.5 mL vial containing 20 Âµg each of HPV-6 L1 and HPV-18 L1 virus-like particles (VLPs) protein, and 40 Âµg each of HPV-11 and HPV-16 L1 VLPs protein [21]. Thus two “batches” of 11 and 16 must be manufactured to match up with the yield from one batch of 6 and 18. These 6 batches are called a set. For reasons explained in Appendix A, a “set” is estimated to yield 15.4 million doses. Cervarix, 0.5 mL vial, contains 20 Âµg each of HPV-16 and HPV-18 L1 VLP proteins [22]. For reasons explained in Appendix A, two batches are estimated to yield a set of 3.6 million doses.

2.3. Raw materials

Based on information made public by Merck and GSK or other sources, we researched in detail the materials, quantities, costs, and patterns of use or reuse needed to manufacture each vaccine (See Appendix A). Actual costs vary by brand and bulk-order discounts. For Gardasil-4, this analysis estimates that the retail costs for all material to manufacture a set of 1.54 million doses are approximately $2.9 million. For Cervarix, the high estimate for materials for 3.6 million doses is approximately $1.27 million. For our sensitivity analysis, we again assumed that large buyers negotiate discounts of 20–40% and used these for the middle and low estimates. These produce a middle estimate of $2.37 million and a low estimate of $1.78 million for Gardasil-4, and $1.02 million and $0.76 million for Cervarix.

2.4. Manufacturing personnel

Based on in-depth studies of other vaccines and specific reports for Gardasil-4 and Cervarix, it appears that both Merck and GSK have approximately 152 personnel involved in manufacturing their vaccines [21]. Staff for manufacturing, quality assurance, and quality control (QA-QC) to GMP standards, filling & packaging, and supervision are included in these estimates and reflect industry and independent information. They are paid on annual salaries, and we estimate the costs of personnel for Gardasil-4 to range between $7.99 and $11.22 million a year and for Cervarix between $6.37 and $8.95 million. (Compensation in France differs from the U.S. See Appendix A.) For the analysis, we used the average of these estimated annual costs for a middle estimate, $9.0 million for Gardasil-4 and $7.2 for Cervarix.

2.5. Factory and administrative overheads

Based on other studies of manufacturing cost [17,18], factory and administrative overhead costs equal 45 percent of the cost
of both raw materials and labor. Sensitivity analysis puts Gardasil-4’s low, middle, and high costs at $4.39, $5.12, and $6.38 million. For Cervarix, the cost estimates are $3.21, $3.69, and $4.59 million.

2.6. Filling and packaging

According to confidential interviews with experts on manufacturing, the wholesale unit cost of the vial, cap, and stopper for single-dose packaging is $0.21 per dose plus $0.10 for secondary packaging materials, for a total of $4.77 million for 15.4 million doses of Gardasil-4 and $1.12 million for 3.6 million doses of Cervarix. The fill/pack staff are included in personnel, and indirect costs are part of overheads. There is no indication that the discounts for these vials themselves are substantial.

3. Results

The estimated low, middle, and high costs of manufacturing per dose is the sum of the total cost divided by volume of doses within a fiscal year. As Table 1 shows, the estimated manufacturing cost for Gardasil-4 ranges from US$2.07 to $3.05 per dose. Manufacturing a second set of 15.4 million doses within a year costs $0.48–$0.59 per dose because fixed capital costs and annual personnel costs are included in the first set (Table 2). Because filing and packaging constitute 58.2% of total costs in the second set, manufacturing the vaccine in ten-dose vials would lower the cost per dose to around $0.21 a dose, or $0.42 for a two-dose course per person (Table 2). Fig. 1 shows the average costs per dose of the first and second sets from Tables 1 and 2. Because per unit costs decline as volume increases, the most important factor in reducing vaccine costs is not a technological breakthrough but “a major increase in procurement…” [18]. This is illustrated in Fig. 2. As shown in Appendix B (worldwide sales and profits), Merck’s sales have steadily risen since 2010 to more than 21 million doses a year.

For Cervarix, the estimated manufacturing costs in the first set of 3.6 million doses ranges from $6.16 to $9.39 a dose in single-dose vials. Table 3 indicates that the average costs per single dose in the second set produced within a fiscal year would drop to US$0.62–$0.82 for single-fill vials. Ten-dose vials would cost $0.24–$0.32 per dose.

Fig. 3 shows the average costs per dose of the first and second sets from Tables 3 and 4. As shown in Appendix B, GSK appears to have sold about 2.1 million doses in 2015, substantially fewer than one set. If first-set costs were attributed to just this volume, the per-unit cost would jump to $10.56–$16.10.

4. Discussion

Based on the best available information from public sources, company reports, and interviews with experts, this study uses sensitivity ranges to estimate the manufacturing costs of Gardasil-4 and Cervarix. For the first set of 15.4 million doses of Gardasil-4, manufacturing costs lie between US$2.07 and $3.05. Manufacturing costs for a second set are about US$0.48–$0.59 per dose. These estimates are well below the price of US$4.50 given to Gavi by Merck.

For this study, an analysis of sales, volume and profits was carried out and is reported in Appendix B. Merck has enjoyed substantial sales and gross profits. From 2006 to 2015, Merck took in about US$13.7 billion from sales of Gardasil-4. Its gross profits more than match any reasonable estimate of past corporate research and development costs incurred for this vaccine, net of taxpayer subsidies [23,24]. Since 2010, Merck’s sales have steadily risen to more than 21 million doses in 2015; so the manufacturing costs for the
second set sold to Gavi and developing countries range between $0.48–$0.59 per dose. Ten-dose vials could lower costs further.

The estimated manufacturing costs of Cervarix for the first set lie between US$6.16 and $9.39 which is well above the price to Gavi. Appendix B shows that from 2006 to 2015, GSK received gross revenues of about US$2.9 billion from Cervarix sales. Its gross profits of $2.6 billion more than covered its past, net corporate costs for research and development. Outside its contract to Gavi, GSK has the most to gain by competing on price against Merck for market share. Thus, even with only two companies, lively price competition could take place. This would make HPV vaccines more accessible, as happened when competition lowered prices for the first generation of HIV-AIDS drugs [25].

Gavi’s leadership has been criticized for not investigating real manufacturing costs and bargaining for lower prices that would be sustainable for its countries [26]. In our view, Gavi and Merck leaders need to re-price Gardasil-4 at $0.59 or less. While Gavi emphasizes vaccine introductions [27], it appears to be meeting little of the overall demand from member countries, which is estimated to rise to 39 million doses a year by 2020 [28,29]. A price at manufacturing cost would greatly increase Gavi’s capacity to vaccinate more children.

Table 3
Estimated costs for producing the first set of 3.6 M doses of Cervarix (2014 million US$).  
|                  | Low estimate | Middle estimate | High estimate |
|------------------|--------------|-----------------|---------------|
| Annualized capital costs | $10.73       | $14.30          | $17.88        |
| Raw materials    | 0.76         | 1.02            | 1.27          |
| Labor            | 6.37         | 7.17            | 8.95          |
| Factory and administrative overheads | 3.21         | 3.69            | 4.59          |
| Filling and packaging, single-dose vials | 1.12         | 1.12            | 1.12          |
| Total costs      | 22.19        | 27.30           | 33.81         |
| Dollars per dose, single-fill | 6.16         | 7.58            | 9.39          |
| Dollars per dose, 10-fill  | 2.40         | 2.96            | 3.66          |

Table 4
Estimated costs for producing the second set of 3.6 M doses of Cervarix (2014 million US$).  
|                  | Low estimate | Middle estimate | High estimate |
|------------------|--------------|-----------------|---------------|
| Raw materials    | 0.76         | 1.02            | 1.27          |
| Factory and administrative overheads | 0.34         | 0.46            | 0.57          |
| Filling and packaging, single-dose vials | 1.12         | 1.12            | 1.12          |
| Total costs      | 2.22         | 2.60            | 2.96          |
| Dollars per dose, single-fill | 0.62         | 0.72            | 0.82          |
| Dollars per dose, 10-fill  | 0.24         | 0.28            | 0.32          |
Despite being cost-effective in most countries [30], globally the burden of HPV cancers and loss of productivity in the prime of life have hardly been touched. In the 33 countries where HPV vaccines are likely to have the greatest benefit, only 4 had introduced national vaccination programs as of January 2012 [2]. Agosti and Goldie estimated a decade ago that “with every 5-year delay in bringing [HPV] vaccination to developing countries, 1.5 million to 2 million more women will die.” [14].

Setting low vaccine prices for Gavi-eligible countries is an important moral commitment by the companies to reduce global health inequities by preventing cancer and deaths in lower-income countries. Merck and GSK have discount and charitable programs that increase access to their HPV vaccines for some countries. Both companies rank high in the global Access to Medicines Index: GSK ranks first and Merck sixth in the world. Both are strong supporters of Gavi. As producers of global public health goods, they need to be transparent about their costs and negotiate prices accordingly. For countries just above the threshold income for Gavi subsidies, the lowest world prices of $12–13 per dose are much higher than what scores of those countries can afford. As Agosti and Goldie wrote, for lower-income countries, “…per-dose cost may need to be as low as $1 to $2…” [14]. This study challenges the manufacturers and Gavi to commence vigorous discussion about how to achieve such prices now and lower prices in the future.

5. Limitations

This analysis has several limitations. While it is based on the best available information, the lack of access to verifiable manufacturing information from the companies has prevented more accurate figures. The high, middle, and low ranges are estimates, and actual costs will depend on the details of each variable in our estimates, such as the manufacturing site, details of manufacturing, the costs of GMP, the number and costs of personnel needed to make each vaccine, and fluctuations in costs of raw materials. This analysis is limited to the two HPV vaccines used by Gavi, and much work is underway to develop cheaper HPV vaccines that are better suited to the realities of vaccination in developing countries.

Authors’ contributions

DWL conceived the project, oversaw it, and co-authored the main text. CC researched the costs and co-authored the main text and Appendix A. YZ researched and drafted the Introduction, and contributed to all aspects of the paper and calculations. RW was involved in the cost calculations, revisions, and served as a senior economic advisor.

Conflicts of interest

Over the period of 2013–2015, DWL’s department received $28,200 from MSF based on a research contract to carry out this research. He received none of this money, but some of it went to general support for his regular salary. He has received no payments from pharmaceutical companies and declares no conflicts of interest.

CC received $1700 from MSF through Rowan University for this research. She has received no payments from pharmaceutical companies and declares no conflicts of interest.

YZ has received no payments from pharmaceutical companies and declares no conflicts of interest.

RNW has received no payments from pharmaceutical companies and declares no conflicts of interest.

Role of the funding source

MSF staff commented on drafts of the final report but did not participate in the study design or analysis. They suggested names of experts in vaccine manufacturing. MSF interns researched the sales, volume, and profit figures in Appendix B. Rowan staff played no role in the study.

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Possible summary

This study finds that manufacturing costs for the most widely used vaccine against cervical cancer are low. It could be affordably priced, with profits, for millions of patients in countries where most cases occur.

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Appendices A and B. Supplementary material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2016.09.042.

References

[1] de Sanjosé S, Serrano B, Castellsagué X, Brotos M, Muñoz J, Bruni L, Bosch FX. Human papillomavirus (HPV) and related cancers in the global alliance for vaccines and immunization (GAVI) countries. A WHO/ICO HPV Information Centre Report. Vaccine 2012;30(Suppl. 4).

[2] MSF. The right shot: extending the reach of affordable and adapted vaccines. 2nd ed. Geneva: Médecins Sans Frontières; 2015.

[3] Arbyn M, Castellsagué X, de Sanjosé S, Bruni L, Saraiya M, Bray F. World-wide burden of cervical cancer in 2008. Ann Oncol 2011;22:2675–83.

[4] Warnakulasuriya S. Global epidemiology of oral and oropharyngeal cancer. Oral Oncol 2009;45:309–16.

[5] Sturgis E, Ang K. The epidemic of HPV-associated oropharyngeal cancer is here: is it time to change our treatment paradigms. J Natl Compr Canc Netw 2011;9:665–73.

[6] Schiller JT, Castellsague X, Garland S. A review of clinical trials of human papillomavirus prophylactic vaccines. Vaccine 2012;30(Suppl. 5):F123–38.

[7] WHO. Human papillomavirus (HPV) and cervical cancer fact sheet. Geneva: World Health Organization; 2016. June.

[8] Lu B, Kumar A, Castellsagué X, Giuliano AR. Efficacy and safety of prophylactic vaccines against cervical HPV infection and diseases among women: a systematic review and meta-analysis. BMC Infect Dis 2011;11. http://dx.doi.org/10.1186/1471-2334-11-1

[9] Van Kruikening C, Castellsague X, Clbula D, Demarteu N. Estimation of the potential overall impact of human papillomavirus vaccination on cervical cancer cases and deaths. Vaccine 2014;32:733–9.

[10] Einstein MH, Baron M, Levin MJ, Chatterjee A, Fox B, Scholar S. Comparison of the immunogenicity of the human papillomavirus (HPV)-16/18 vaccine and the HPV-6/11/16/18 vaccine for oncogenic non-vaccine types HPV-31 and HPV-45 in healthy women aged 18–45 years. Hum Vaccines 2011;7:1343–58.

[11] Gavi. Human papillomavirus vaccine support. Geneva: Gavi - the Vaccine Alliance; 2015.

[12] WHO. Table 1: summary of WHO position papers - recommendations for routine immunization. Geneva: World Health Organization; 2015. Feb.

[13] Mukhopadhyay P, Bhaskar P. Introducing HPV in developing countries - addressing the challenge. Indian J Commun Med 2009;34:370–1.

[14] Agosti JM, Goldie SJ. Introducing HPV vaccine in developing countries - key challenges and issues. N Engl J Med 2007;356:1908–10.

[15] Herdman C, Dempsey M. Introducing HPV vaccines in developing countries: overcoming the challenges. Seattle: Program for Appropriate Technology in Health (PATH); 2005.

[16] McNeil DJ. Cancer vaccines get a price cut in poor nations. In: The New York Times. New York: The New York Times; 2013. May 9.

[17] Mahoney RT, Francis DP, Frazatti-Gallina NM, Precioso AR, Raw I, Watler P, et al. Cost of production of live attenuated dengue vaccines: a case study of the Instituto Butantan, Sao Paulo, Brazil. Vaccine 2012;30:4892–6.

[18] Mahoney RT. Cost of plasma-derived hepatitis B vaccine production. Vaccine 1990;8:397–401.

[19] Smith J, Lipsitch M, Almond J. Vaccine production, distribution, access and uptake. Lancet 2011;378:428–38.

[20] UNIDO. Manual for the preparation of industrial feasibility studies. Vienna: United Nations Industrial Development Organization; 1995.

[21] CHMP. Silgard: EPAR - scientific discussion. London: EMA (European Medicines Agency); 2006.

[22] RxList Inc., Cervarix; 2014.

[23] Light DW, Warburton RN. Demythologizing the high cost of pharmaceutical research. Biosocieties 2011;6:34–50.

[24] Grager S, Guilien E, Price M. University contributions to the HPV vaccines and immunization (GAVI) countries. A WHO/ICO HPV Information Centre Report. Vaccine 2012;30(Suppl. 4).

[25] UNICEF. UNICEF procurement advancements. UNICEF supply chains for闽南 leases. Geneva: UNICEF; 2016. June.

[26] UNICEF. UNICEF procurement advancements. UNICEF supply division. Human papillomavirus vaccine supply & demand update. Paris: UNICEF Supply Division; 2015 [July].

[27] Gavi. The vaccine alliance progress report 2014: summary. Geneva: Gavi - the Vaccine Alliance; 2014. p. 2015.

[28] UNICEF supply division. Human papillomavirus vaccine supply & demand update. Paris: UNICEF Supply Division; 2015 [July].

[29] UNICEF. UNICEF procurement advancements. UNICEF supply chains for children, Paris: UNICEF; 2013 [Oct].

[30] Jit M, Brisson M, Portnoy A, Hutubessy R. Cost-effectiveness of female human papillomavirus vaccination in 179 countries: a PRME modelling study. Lancet Global Health 2014;2:e408–14.