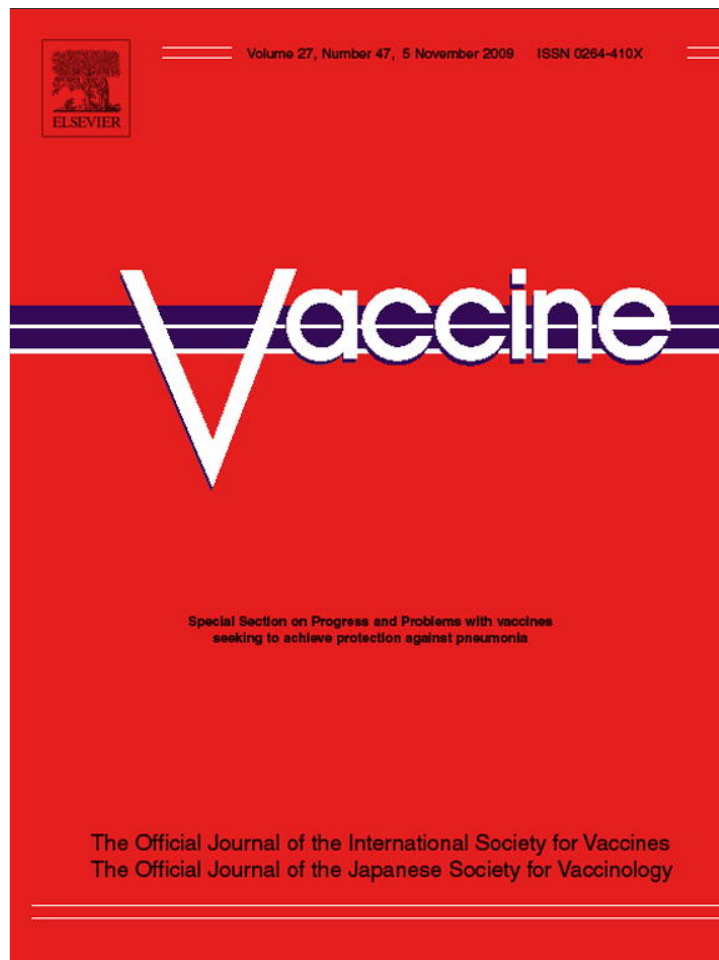


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Estimated research and development costs of rotavirus vaccines

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ABSTRACT

Diseases like rotavirus afflict both upper- and lower-income countries, but most serious illnesses and deaths occur among the latter. It is a vital public health issue that vaccines for these types of global diseases can recover research and development (R&D) costs from high-priced markets quickly so that manufacturers can offer affordable prices to lower-income nations. Cost recovery depends on how high R&D costs are, and this study attempts to replace high, unverified estimates with lower, more verifiable estimates for two new vaccines, RotaTeq (Merck) and Rotarix (GlaxoSmithKline or GSK), based on detailed searches of public information and follow-up interviews with senior informants. We also offer a new perspective on “cost of capital” as a claim for recovery from public bodies. Our estimates suggest that companies can recover all fixed costs quickly from affluent markets and thus can offer these vaccines to lower-income countries at prices they can afford. Better vaccines are a shared project between companies and public health agencies; greater transparency and consistency in reporting of R&D costs is needed so that fair prices can be established.

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1. Introduction

Rotavirus globally is estimated to cause 111 million episodes of gastroenteritis, 25 million clinic visits, 2 million hospitalizations, and 440,000 deaths in children aged <5 years. Children of the poorest countries account for 82% of the deaths. Models used to estimate the burden of rotavirus globally have generated estimates for Latin America of 15,000 deaths, 75,000 hospitalizations, 2 million clinic visits, and 10 million cases of diarrhea [1,2]. Therefore, an important breakthrough for lower-income countries is the discovery and successful testing of two vaccines for rotavirus. Since governments with very limited budgets for health care and public health will be buying these vaccines, setting an affordable price will be critical for lifting the burdens of this disease.

A classic dilemma for pharmaceutical companies is that lower-income countries can only afford vaccines at a fraction of prices in affluent countries, making it difficult to recover large costs for

research and development (R&D) and make a reasonable profit. As a result, many multinational firms have abandoned the vaccine field. Merck and GSK, however, have remained committed, and it is important that they recover their R&D costs and earn a reasonable profit to fund future vaccine development. However, R&D costs are not publicly disclosed; common estimates by industry-supported studies are based on drugs, rather than vaccines, and are reported to be in the range of \$0.8–\$1.7 billion [3–6].

This study used detailed searches of reports on development and interviews with principal figures to assemble the first independent estimates of R&D costs for two new vaccines, RotaTeq produced by Merck, and Rotarix produced by GSK. The cost figures provide a basis for discussing the setting of sustainable prices for lower-income countries. We first provide important background information to be considered when trying to estimate R&D costs independently, using rotavirus vaccines as the basis for discussion. We then present the results of our study. We close with a discussion of policy implications.

1.1. Background – putting rotavirus vaccine R&D costs in perspective

Since the 1960s, the high risks, costs, and delays inherent in research and development for a new drug (or vaccine) have been the principal reasons that pharmaceutical companies have given

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for needing to price their products 40–100 times more than their ongoing costs of production [7]. The classic argument consists of three basic propositions [8]. First, pharmaceutical research is very risky: only 1 out of every 5000–10,000 compounds screened is ultimately approved for sale by the Food and Drug Administration (FDA). Second, R&D costs are very high. Third, R&D costs represent opportunity costs that have to be sustained over 10–15 years, when a firm could have retired debt or invested the money (e.g. in an equity fund) and earned a good return. Thus, the total cost for a new product consists of both direct costs plus cost of capital, or profits foregone.

The classic argument requires further scrutiny. As it stands, public and elected leaders in the position of negotiating affordable prices for a societal good are confronted with claims of very high R&D costs without evidence that has been independently verified or audited. This study aimed to obtain the most authoritative evidence of actual R&D costs so that more informed negotiations could take place to seek affordable prices for lower-income populations by special purchasing bodies such as the PAHO Revolving Fund.³

1.1.1. Putting high risk into perspective

Putting the high ratio of 1 out of 5000–10,000 compounds screened being approved for sale next to the estimate of \$802 million–\$1.7 billion in total costs may leave the impression that companies put a great deal of money into high-risk development projects which rarely succeed. However, the initial screenings of 5000–10,000 compounds are done using advanced technology for a relatively small cost [9]. Short lists of likely candidates are further tested and developed, also for a relatively small percentage of total R&D cost, resulting in a small number of candidates that seem both effective and safe enough to take to Phase I trials. At this point, most “failures” have been identified at low cost, and the chance of success through all the human trials is roughly to 1:10 to 2:10 [10]. Overall, 75% or more of all costs occur during human trials, most during Phase III trials, when the risk is low [6,11]. Most of the costs are incurred in Phase III trials, where the chance of success is roughly 1 in 2 or 1 in 3, not 1 in 5000 or 10,000 [10].

Pure product failures are not the only cause of trial failures. A company may wish to withdraw their candidate product because the profit potential may have declined, or because more commercially urgent or promising projects lead to a shift in priorities. Trial results may be mixed, or concerns may have arisen about adverse effects and potential liability. Such withdrawals by companies, whether for commercial or clinical reasons, appear to have increased over time [12]. Companies try to withdraw candidates as early in a phase as possible so that not all the projected costs of that phase are incurred.

To summarize, the financial risk of a given project is lower than broad averages would suggest, and the risk of R&D overall for large companies is lower than for any given project, because they use portfolio management to spread their risks over many projects and potential products. Some critics claim that the R&D rationale to justify high prices provides a strong incentive for companies to keep their costs confidential and to claim that costs are much greater than independent sources suggest [13].

1.1.2. Putting long development time into perspective

It is widely believed and repeated that it takes 12–15 years to discover and develop a new medicine. The most authoritative report, however, based on the only large sample (180 drugs) in which companies reported the day they applied to the FDA to begin

trials, to the day their Phase III trials ended, found that total time declined from nearly 6 years in 1992 to only 3.5 years in 2002 [14,15]. Total time from the IND (FDA approval to start trials) to final market approval declined from almost 8 years in 1992 to less than 5 years in 2002, and has declined further since [14]. A few products have much longer times, which raises the mean, but these delays are as often caused by companies choosing to delay testing by FDA review panels for safety or other regulatory reasons [10,16]. Companies have considerable control over how quickly or slowly they proceed. When the FDA contributes to a longer development time, it is due to serious questions about the efficacy or safety of a drug. Thus in both cases, delays occur for good reasons, and the existence of long-delayed outliers means that the median time would be more representative of average experience than the mean time.

The time for basic research to discover and develop a medicine to the point of applying to begin trials varies widely, from 3 months to 30 years. No empirical study has been done, in part because it often is unclear how far back one should go to the beginning of “basic research,” and in part because there are often several strands of research that contribute to a final discovery. Nor is it always clear how one should allocate the costs and time of basic research work to a specific product. Thus, the most accurate conclusion is that R&D for a new medicine takes a highly variable amount of time up to trials, plus about 5 years.

1.1.3. Putting total costs into perspective

Since the 1970s, the pharmaceutical industry has provided funding and confidential cost data to economists who have developed methods for attaining high estimates of research and development costs [11,17]. Recent total estimates of average costs range from \$802 million to \$1.7 billion per new drug. The most widely cited study of cost concluded that R&D costs for truly new drugs (the FDA term is “new molecular entities” or NMEs) discovered and developed in-house in 2000 was \$802 million [6]. This study, however, relied on self-reported, non-random, unverifiable industry cost figures that were analyzed by researchers associated with the leading industry-funded policy research center [18–21].

In the above study, companies reported average gross costs per NME for clinical trials of \$87 million. Self-originated NMEs are the most costly subset of new drugs approved by the FDA (just 22% of approvals), which adds an upward bias to the mean compared to the median, as do a few very expensive cases. Thus the median would be more representative, and more useful still would be to report a range rather than a point estimate. These reported costs were then augmented by estimated costs inserted for basic research and the cost of failures (assumed to be 79.5% in the sample), which raised the average cost per approved drug to \$403 million. Finally, the “cost of capital” was added, nearly doubling costs to \$802 million. The “cost of capital” is not a real out-of-pocket expense, like interest on a loan, but rather the estimated profits foregone by using funds for drug development rather than simply investing them, based on a notional 11% compound rate of return.

While estimating profits forgone is a useful calculation for making investment decisions, their inclusion in total R&D costs as a claim against public bodies and society is questionable. These companies need to innovate to maintain profits; they are not in the business of simply investing funds. In addition, R&D costs are treated by the IRS as a normal business expense that is deducted from gross income annually, reducing current taxes; but tax savings are not reflected in the \$802 million figure. Thus the methods developed to convert \$87 million to \$802 million are not without controversy and have been the subject of published critiques by ourselves and others [13,18,19]. Any estimate of returns on investment before the fact might more usefully be regarded as a goal, rather than a guarantee or claim on society.

³ The PAHO Revolving Fund is the bulk purchasing mechanism through which member countries in the Americas procure their vaccines and immunization supplies.

In addition, the 11% rate of return used in the above study is much higher than the usual discount rates of 3–7% recommended in government cost-benefit guidelines [22,23]. The 11% rate is often stated to be based on the pharmaceutical industry's expected rate of return, but in the real world of competitive markets, profits are never guaranteed; had a company invested in the American Exchange Pharmaceutical Index of stocks in December 1998 at \$368, its value was \$260 10 years later, an annual average loss of 3.4%.

For the above reasons, we believe that the median costs of R&D to companies for all new drugs after tax deductions and credits is probably one-sixth of costs claimed for NMEs [24]. Yet the estimates of \$802 million, and now \$1.3–\$1.7 billion, are widely claimed to be the average R&D costs for any new medicine. It would be more informative for public policy if companies reported their actual R&D costs for new vaccines; these are societal goods purchased largely from public funds.

2. Methods for estimating R&D costs

Instead of using economic modeling or previously reported cost figures, we undertook an empirical approach grounded in economic sociology. Searches were conducted using five sources: the U.S. Patent and Trademark Office, the U.S. SEC EDGAR database, Medline, periodicals, and corporate websites. In order to develop a detailed picture of how each vaccine was developed, the location of work, length of phases, types of testing, number of trials, sizes, and locations was collected, so that we could interview informants in a detailed, ground-up way about what various processes and phases cost. U.S. patents with titles containing the keywords 'vaccine' and 'rotavirus' were identified and reviewed using the U.S. Patent and Trademark Office search engine (19 results). Targeted searches within these results were undertaken using search terms related to the various vaccine developers (Ward, Bernstein, Cincinnati, Clark, and Wistar). Using a complementary approach, the corporate financial filings (10-K) to the U.S. Securities and Exchange Commission for GlaxoSmithKline, Avant Immunotherapeutics, and Merck & Co were also searched using "rotavirus," "89-12," vaccine," and "rotarix" for GSK and Avant, and "rotateq" for Merck. R&D spending data from the filings were compiled into an Excel spreadsheet (for Avant and GSK only: data not reported by Merck). As a third data source, the Medline database was used to identify relevant peer-reviewed literature using combinations of "rotavirus vaccine," "attenuated," "monovalent," "trial," "Cincinnati," "89-12," "RIX4414," "Glaxo," and "Avant." Fourth, relevant articles in the Wall Street Journal, New York Times, and trade periodicals were identified by searching LexisNexis Academic and ProQuest databases for 'rotavirus' and 'vaccine'. Finally, the Cincinnati Children's Hospital, GlaxoSmithKline, and Avant Immunotherapeutics, Children's Hospital of Philadelphia, Merck & Co., Sanofi Pasteur, and Wistar Institute websites were searched for press releases and other information regarding the RotaTeq and Rotarix vaccines.

Information from these searches overlapped considerably and was used to cross-validate a detailed listing of all phases of research and trials, including the phase, size, ages of subjects, location, year, and number of centers, as well as the officers, investigators, and authors involved. These accounts are summarized in the following pages. Senior officers and investigators who were most likely to know the budgets for each phase, were approached by telephone and email, explaining the project and requesting a telephone interview anywhere in the world to discuss the details of developing and testing these vaccines. An outline was carefully prepared from the detailed accounts of questions to ask about missing details, time and resources. This approach provided the basis for constructing a semi-structured interview schedule that asked key informants to explain the organization and steps involved

in doing the trials, which then was used as the basis for asking about costs. Seven of eleven senior researchers and officers approached agreed to be interviewed. Interviews were conducted in December 2005–February 2006 and lasted 20–40 min. These conversations sometimes led to others being recommended for interview about certain other research costs. The goal was not representative sampling, since there was no clear universe on which to sample; but rather to reach a high level of consistency and congruence between the various sources of information including informed interviewees' estimates of costs. Interviewees varied somewhat in their estimates of costs, which is reflected in our low and high estimates for total clinical and administrative costs per patient.

3. Results – trial history and costs

Table 1 shows reported trial dates, sizes, and costs for RotaTeq and Rotarix that were published and/or submitted to regulators. Merck's RotaTeq vaccine is a pentavalent (active against five rotavirus strains: G1, G2, G3, G4, and P1) bovine-human reassortant vaccine created by combining human rotavirus genes

Table 1
Trial information – RotaTeq and Rotarix (total costs in Million U.S. Dollars).

	Year	N	Low estimate	High estimate
Unit cost (U.S. Dollars)				
Phase I			\$100	\$400
Phase II			\$300	\$400
Phase III			\$2,000	\$3,000
RotaTeq – Merck				
Phase I				
Clark	1987	104	\$10,400	\$41,600
Garbag-Chenon	1988	25	\$2,500	\$10,000
Bernstein	1989	206	\$20,600	\$82,400
Treanor	1994	325	\$32,500	\$130,000
Total Phase I		660	\$66,000	\$264,000
Phase II				
Vesikari	1998	1,946	\$583,800	\$778,400
Clark	1997	731	\$219,300	\$292,400
Clark	1993	439	\$131,700	\$175,600
Total Phase II		3,116	\$934,800	\$1,246,400
Total Phases I & II		3,776	\$1,000,800	\$1,510,400
Phase III				
Vesikari	2001	68,038	\$136,076,000	\$204,114,000
Total Phase III		68,038	\$136,076,000	\$204,114,000
Total All Phases		71,814	\$137,076,800	\$205,624,400
Rotarix – GSK				
Phase I				
Bernstein	1995	125	\$12,500	\$50,000
Vesikari	2003	251	\$25,100	\$100,400
Total Phase I		376	\$37,600	\$150,400
Phase II				
Bernstein	1997	215	\$64,500	\$86,000
Bernstein	1999	184	\$55,200	\$73,600
Vesikari	2000	405	\$121,500	\$162,000
Phua	2001	2,464	\$739,200	\$985,600
Salinas	2001	2,155	\$646,500	\$862,000
Dennehy	2000	529	\$158,700	\$211,600
Total Phase II		5,952	\$1,785,600	\$2,380,800
Total Phases I & II		6,328	\$1,823,200	\$2,531,200
Phase III				
Ruiz-Palacios	2003	63,225	\$126,450,000	\$189,675,000
Total Phase III		63,225	\$126,450,000	\$189,675,000
Total All Phases		69,553	\$128,273,200	\$192,206,200

Notes: N = number of subjects. Unit cost = reported mean dollars spent per subject. *No verified evidence that new facilities had to be built after Phase III trials; if built, costs estimated at \$200 million.

with WC3 cow virus [25], administered in three doses. The vaccine was created by Dr. H. Fred Clark of the Wistar Institute of the University of Pennsylvania and Dr. Paul Offit, Chief of Infectious Diseases at the Children's Hospital of Philadelphia (CHOP). Merck licensed the RotaTeq vaccine from CHOP and initiated a 1992–1993 efficacy trial ($N=325$) [26] with Drs. Clark and Offit as primary investigators. Thus all costs and risks from discovery up to this trial preceded Merck's involvement and are reflected in royalties from revenues after approval, rather than at-risk R&D investment. This trial led to a 1993–1994 blinded, randomized, placebo-controlled proof-of-concept trial in 439 infants aged 2–6 months old [27]. After Wyeth withdrew its RotaShield vaccine in 1999, Merck accelerated its testing. In March 2001 Merck began the double-blind, randomized, placebo-controlled "Rotavirus Efficacy and Safety Trials" (REST trial) which was believed to be large enough to conclusively demonstrate the efficacy of RotaTeq and to rule out increased intussusception risk [28]. This required enrolling 68,000 infants in eleven countries (mainly the U.S. with 33,000 and Finland with 23,500) [25]. The REST trial tested RotaTeq administered at 2–3 months followed by two subsequent doses, each 1–2 months after the last. With the successful results, RotaTeq was licensed.

GlaxoSmithKline's Rotarix was developed by Dr. Richard Ward and Dr. David Bernstein at Cincinnati Children's Hospital Medical Center in the early 1990s. Rotarix, which was labeled '89-12' early in its development, is an oral live attenuated human vaccine administered in two doses [29]. Unlike Rotashield or Merck's RotaTeq, Rotarix is a single strain (monovalent) vaccine which means it specifically protects against one variety of rotavirus (G1) and induces some cross-protection against other varieties (G3, G4, and G9) [30]. Rotarix is also unique among other rotavirus vaccine candidates in being a human rather than a rhesus or bovine reasortant virus [25]. Dr. Ward received a patent in 1995, assigned to the James N. Gamble Institute of Medical Research, now part of the Cincinnati Children's Hospital's Division of Infectious Diseases).

In 1995 Children's Hospital entered a licensing agreement with the Virus Research Institute, which merged with T Cell Sciences in August 1998 to form Avant Immunotherapeutics (Needham, MA) [29]. Avant funded a Phase II clinical trial of Rotarix from August 1997 to June 1998 with Dr. Bernstein, now a consultant to Avant as well as a researcher at Cincinnati Children's Hospital, as principal investigator [31]. This trial proved 89% protection and few adverse events, and Avant completed a 2-year extension in May 2000 which showed effectiveness remained after two years from inoculation. Glaxo (then, SmithKline Beecham) negotiated worldwide marketing rights in 1997 in return for assuming all development costs, paying Avant \$5.5 million in milestone payments, and royalties of about 10% on net sales [29]. Thus all costs and risks from discovery up to this point preceded Glaxo's involvement and are reflected in milestone payments after risk is low, plus royalty payments after revenues commence. Glaxo completed I/II bridging and Phase II trials in 2002 [32]. It then initiated a Phase III trial of 63,000 children aged 6 weeks to 6 months in Latin America and Finland in the third quarter of 2003. The Phase III trial is billed by GlaxoSmithKline Biologicals as the 'largest infant vaccine trial ever conducted' [33].

3.1. Phase I trials

Organizational and financial data on Phase I trials are reported less than on other phases, and when reported are less complete. However, their contribution to R&D costs is small and therefore this data weakness does not significantly affect overall cost estimates. Investigators for both vaccines said that Phase I trials for safety were simple, small, and inexpensive. They consisted of an injection and simple follow-up procedures. Adults or parents/guardians

then reported on diary cards any from a list of adverse symptoms they observed. Investigators estimated in interviews that total costs including set-up, administration, and support averaged from \$100 to \$400 per subject. Our searches documented trials including 660 subjects for Merck, and 376 for GSK. Thus, the range of estimated costs were about \$66,000–\$264,000 for Merck, and about \$37,600–\$150,400 for GSK. As in all raw cost estimates, these are uncorrected for inflation, cost of capital, or failure of other vaccines projects.

3.2. Phase II trials

These trials are longer, but senior investigators interviewed explained that most of the additional time consisted of parents monitoring their infants for a longer period. One interviewee noted:

"Monitoring was mainly by parents calling to say their infant has a symptom, usually gastrointestinal problems. The parents must take a stool sample." Jan 24, 2006

Another interviewee said:

"The mothers are the front-line sentinels. . . .we told them that if symptoms arose to do what they normally do. . ." Jan 26, 2006

For recruitment and testing, the companies drew on physicians who were already known and had a track record of doing a good job of recruiting, administering, and providing accurate, reliable reports in past trials. Recruitment of toddlers and infants is relatively easy for the physicians responsible for the infants, interviewees said, thus avoiding large recruitment costs. The mothers/parents have usually chosen their physician to care for their offspring and trust him or her so that the drop-out rate of infants is low. All of these features considerably lowered trial costs compared to trials with adult subjects.

Total costs for administration, recruitment, management and assays were estimated to average \$300–\$400 per subject. We found 6 trials for GSK with a total of 5952 subjects, and 3 trials for Merck with a total of 3116 subjects. Thus the estimated Phase II costs were \$0.9 million–\$1.2 million for Merck, and \$1.8 million–\$2.4 million for GSK. We are unaware of other studies needed for submission to regulatory authorities.

3.3. Phase III trials

Senior researchers and officers involved in the trials consistently reported that the size of Phase III trials for vaccines usually involve 5000–6000 subjects; but because of the previous withdrawal of Wyeth's RotaShield vaccine from the U.S. market [34] and the need to make the trials large enough to rule out a rare but potentially fatal side effect (intussusception), these trials ranged from 63,000 to 68,000. Setting up trials across all sites and countries took many months. Investigators and teams had to be recruited, and centers had to be identified to which parents would take their babies if symptoms arose. Recruitment in each country followed the same procedure of using pediatricians already known for doing good work in previous trials and having them recruit the parents of infants. This reduced costs significantly. However, in these countries extra time had to be spent with both parents to coach them in monitoring and managing their child's symptoms over many months. Smaller sub-trials measured other side effects.

Senior researchers and officers estimated from \$2000 to \$3000 for total costs per subject in wealthy countries. This range-estimate would apply to sites used by Merck, while GSK used many sites in developing countries where costs were less. But if one applies this higher range to both companies, the total Phase III estimated costs range ranged from \$136.1 to \$204.1 million for Merck, and \$126.4 to \$189.7 million for GSK.

3.4. Total costs

The total costs for Phase I–III trials were \$137–\$206 million for Merck and \$128–\$192 million for GSK. Adding in cost of capital, or profits foregone, does not raise these cost estimates very much, because most of the cost occurred near the end of the development project. By contrast, industry-supported sources claim that the Phase III trial alone cost \$350 million, and total R&D costs are widely believed to exceed \$1.0 billion per new product [3]. These claimed costs differ substantially from our estimates.

3.5. Manufacturing capacity and costs attributable to R&D

Generally, the people interviewed about manufacturing were regarded as leading experts with long experience working for major pharmaceutical companies but now working independently. They told us that these two vaccines did not pose technical manufacturing challenges for GSK and Merck because both companies have experience in making vaccines of these kinds and had already manufactured them in volume for the large Phase III trials. People interviewed in some cases disputed reports that either company had to build a new factory to manufacture these vaccines. Given the new, rapidly expanding era of highly profitable vaccines, they said, it is difficult to know which parts or portions of expanded capacity can fairly be attributed to a given vaccine. If a new plant costing \$200 million produces 100 million doses a year over the plant life of 15 years, the capital costs per dose would be small, and clearly the entire plant cost should not be attributed to any one vaccine.

Given that a company must manufacture a vaccine for its trials, should these costs be attributed to R&D or to manufacturing tool-up? One expert explained that the technology and assay costs of development for these two vaccines were done before and during the clinical trials and thus intertwined with R&D costs. Factors minimizing manufacturing costs are summarized in Wainwright's comprehensive analysis of the subject:

The production processes and test methods for the manufacture of rotavirus vaccines are well understood, and compared to many production processes, they are straightforward and have been used previously to make other vaccines. Consequently, global vaccination against rotavirus disease should not be hampered by lack of vaccine candidates, lack of safety and efficacy experience, lack of acceptance in developing countries, nor lack of manufacturing expertise. . . . Because the costs of vaccines are

inversely proportional to the volume of vaccine produced, it will be incumbent on the countries in need to establish manufacturing capability. Keeping the manufacturing process, formulation, and delivery devices simple and easy to transfer around the globe will be essential to achieving global vaccination [35,4].

Regarding the direct relevance of preclinical and early trial costs for developing successful manufacturing capacity, Wainwright points out that data from the first preclinical batch produced onward contribute significantly to developing successful manufacturing that will also secure approval by the countries involved. Developing the different kinds of assays is critical, but also starts very early. Entire sections of his detailed report are devoted to preclinical milestones for manufacturing: building a successful platform of processes to address purity, stability, quality assurance systems; preparing clinical protocols; being able to manufacture high-quality and consistent buffers and media solutions; carrying out stability studies; and finding or building a facility that will meet standards for product registration.

Experts interviewed estimated costs of \$100–\$200 million for multinationals like GSK and Merck to establish manufacturing capacity and “scale up” production for large Phase III clinical trials. These figures are substantially higher than facility costs for FDA-approved, high-quality manufacturers in developing countries. We concluded it was best to estimate high and low R&D costs, assuming no new plant was built (low cost), or assuming a \$200 million plant was built (high cost).

3.6. Total estimated costs and cost of capital

As shown in Table 1, before the exceptionally large Phase III trials, R&D cost estimates ranged from \$1.0 to \$1.5 million for Merck, and \$1.8 to \$2.5 million for GSK. Adding in Phase III trials brought the totals up to \$137–\$206 million for Merck's RotaTeq and \$128–\$192 million for GSK's Rotarix. Estimated R&D costs are substantially lower than the \$350 million claimed by Merck-related interviewees for Phase III trials.

Table 2 adds together trial costs and manufacturing capital costs, and shows in columns 1 and 2 the actual costs, and inflation-adjusted costs (in 2008 U.S. Dollars). Total costs are estimated to have ranged between \$137 and \$539 million for Merck's RotaTeq, and \$128 and \$392 million for GSK's Rotarix. The range is larger than for trial costs, because the higher estimates include \$200 million for each company, for possibly building new manufacturing capacity. Since this expenditure could not be verified, the low esti-

Table 2
Estimated trial and development costs, including cost of capital – RotaTeq and Rotarix (Million U.S. Dollars).

Phase	Actual cost		Cost in 2008 Dollars ^a		Low capitalized cost, 2008 Dollars (3% rate)		Medium capitalized cost, 2008 Dollars (5% rate)		High capitalized cost, 2008 Dollars (7% rate)	
	Low estimate	High estimate	Low estimate	High estimate	Low estimate	High estimate	Low estimate	High estimate	Low estimate	High estimate
RotaTeq – Merck										
Phase I	0.1	0.3	0.1	0.2	0.1	0.4	0.2	0.6	0.2	0.9
Phase II	0.9	1.2	1.3	1.7	1.7	2.3	2.2	2.9	2.7	3.6
Phase III	136.1	204.1	165.4	248.1	203.5	305.2	232.8	349.2	265.6	398.5
Mfg. Capital	0.0	200.0	0.0	257.6	0.0	336.3	0.0	400.2	0.0	474.8
Total – Merck	137.1	405.6	166.7	507.6	205.3	644.3	235.1	752.9	268.5	877.8
Rotarix – GSK										
Phase I	0.0	0.2	0.0	0.2	0.1	0.2	0.1	0.3	0.1	0.3
Phase II	1.8	2.4	2.2	2.9	0.7	0.9	0.8	1.0	0.9	1.2
Phase III	126.5	189.7	148.0	221.9	171.5	257.3	188.8	283.3	207.5	311.3
Mfg. Capital	0.0	200.0	0.0	241.2	0.0	292.4	0.0	331.4	0.0	374.8
Total – GSK	128.3	392.2	150.2	466.3	172.2	550.8	189.7	616.0	208.5	687.7

^a Adjusted using U.S. all-urban CPI.

mate excludes this cost. In 2008 dollars, these costs are equivalent to \$167–\$508 million for Merck, and \$150–\$466 million for GSK.

An important question concerns how much to add for profits foregone (cost of capital) due to the timing delay between R&D costs and sales revenues. As explained above, there are good reasons to maintain that while such estimates are a common tool for making investment decisions, they should not be an automatic claim on society. For purposes of this study, we have estimated cost of capital using three rates. U.S. Government guidelines [22] call for a 7% real discount rate for regulatory decisions affecting primarily private investment, and a 3% real rate for programs affecting primarily consumer prices or spending. In health care, economists commonly use real social discount rates between 3% and 7% [23]. Table 2 uses these rates to provide high (7%), medium (5%), and low (3%) estimates of capitalized costs. Given the pharmaceutical industry's long-standing use of high estimates of R&D costs to support patent legislation (a public policy measure that confers temporary monopoly rights), we believe that in this context it would be more appropriate to use either 3% or 5%.

For Merck, the inflation-adjusted, capitalized total R&D costs (3% discount rate) are estimated to range between \$205 and \$644 million. For GSK, the inflation-adjusted, capitalized (at 3%) total R&D costs are estimated to range between \$172 and \$551. These are large costs, but the detail shows how much of the R&D costs were related to the unusually large Phase III trials for these vaccines – costs that most vaccines do not require.

4. Discussion

This study provides new evidence relevant to the literature and policy concerning pricing of vaccines for lower-income populations. R&D costs need to be recovered in order to provide an incentive for discovery and commercialization of new vaccines, but in order for vaccine purchasers to make well-informed decisions, they need to know the relevant R&D costs. Broad, generalized cost estimates for “average” new drugs are not necessarily relevant or informative because there is great variation in the costs across different drugs. Based on reports from senior investigators and independent evidence, we have assembled evidence that R&D costs to the companies for rotavirus vaccines were much lower than commonly-touted average costs, even though the Phase III trials were much larger than usual. We also presented reasons why cost of capital, while a legitimate concept for making investment decisions, should either not be a part of cost estimates on societal goods or should (for public policy purposes) be calculated at officially established social discount rates (3–7%), rather than market-return-based estimates.

This case study has several limitations that stem from the undisclosed and closely held costs of developing vaccines. Although the independently-estimated R&D cost figures reported here reflect the knowledge of persons involved, and are, we believe, the most accurate cost estimates published to date, none of the cost estimates can be verified. They do suggest caution in accepting company claims of high R&D costs, unless those claims are backed by independently-verified data. We made no estimates related to the costs of failures for other, similar vaccines, because we had no information on failures; however, as noted above the costs of failures should (for most vaccines) be very low, because failures occur largely at or near discovery, or in low-cost Phase 1 trials. In this study, we found that over 98% of all trial costs for RotaTeq and Rotarix occurred in Phase III trials.

Because vaccines are societal goods and largely paid for by taxpayers, and because they are a vital tool in reducing the burden of disease that impedes economic development, their R&D costs should be reported by companies, independently audited, and a common methodology for reporting should be developed. This

would provide transparency and allow fair, affordable prices to be negotiated for purchasers at different income levels.

In this research, we estimated that sales in affluent countries would total about \$400 million in 2007 and \$1 billion or more from 2008 on. We estimated that efficient manufacturing costs were \$6 per 3-dose course for Merck and \$4 per 2-dose course for GSK, marketing to governments was 7% of gross sales, and overheads attributable to these vaccines 4% of sales; these costs would consume no more than 15% of revenues. Thus we estimated total gross profit for the two companies (combined) at about \$340 million in 2007 and \$850 million or more in 2008 and subsequent years. Even after deducting royalty payments and taxes, it seems clear that both companies should have recovered more than their out-of-pocket R&D costs with one year's profits. Even costs of capital would be more than recovered by the second year or no later than the third year on the market. We recommend that companies reduce vaccine prices to production costs plus reasonable profits [36] for lower-income countries or public health international organizations purchasing for them. This will ensure that those most in need have equitable access to these life-saving products.

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