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Sanofi Pasteur: The Dengue Vaccine Dilemma

We are not just selling a product. We are trying to deal with a public health issue. It is about dengue, not only about a dengue vaccine.

— Chris Viehbacher, CEO, Sanofi Group

It was a hot, humid afternoon in June 2012 in Bangkok, Thailand. Jean Lang, associate vice president of R&D at Sanofi Pasteur, the largest company in the world devoted entirely to human vaccines, was nervously staring at his cell phone waiting for a text message to appear. For over two decades, Sanofi Pasteur had raced to develop a vaccine against dengue, a mosquito-borne disease also called breakbone fever, and was currently evaluating this product in a Phase IIb trial conducted with schoolchildren in Thailand. With 50 million to 100 million infections, half a million severe cases, and 25,000 deaths[a] annually, according to the World Health Organization (WHO),[1] the dengue virus was the leading cause of hospitalization and death among children in endemic countries. Sanofi's dengue candidate vaccine was the world's most advanced so far and could represent a major breakthrough in the public health community if the trials confirmed its efficacy. As Lang was awaiting trial results, looking forward to a text message with a smiley face, his phone suddenly rang instead. "Jean, can we talk? We have a problem," the voice said slowly.

Soon thereafter, Guillaume Leroy, vice president of the Dengue Company, a core group of Sanofi Pasteur employees dedicated to dengue vaccine development, surveyed the trial documentation that covered his office desk in Lyon, France. The report indicated that while the candidate vaccine met the high safety expectations and provided reasonable immunity, it had a proof of efficacy of only 30%, far below the 70% mark the company had targeted. The trial's surprising outcome was due to the vaccine's unexpected failure to protect against one of four dengue virus strains, which turned out to be the prevalent one in Thailand at the time of the study. Leroy immediately scheduled a series of meetings with his team to determine which response would allow the company to address the trial's lackluster results.

[a] Data points on dengue showed significant, unexplained disparities, depending on sources and even within a given source. For example, WHO estimated that there were from 50 million to 100 million new dengue infections per year, though other estimates reached as high as 390 million infections. Similarly, while WHO estimated that 500,000 people with severe dengue required hospitalization each year, other estimates reached as high as 96 million severe infections.

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To date, Sanofi Pasteur had dedicated significant resources toward the vaccine's development. In addition to a large upfront investment in R&D, Sanofi Pasteur spent $398 million[2] on a new French factory to produce the vaccine. The company had also implemented an innovative organizational model by creating the dedicated vertical Dengue Company within Sanofi Pasteur. The trial's results left uncertain the future of a product that Sanofi had hoped to make available in the market as soon as 2015 and was estimated to generate $2.6 billion in yearly sales.[3]

The questions Leroy and his team were facing were both strategic and immediate. Should the company continue its Phase III larger-scale trials and conduct a meticulous investigation before making a decision, given the context of the expanding dengue disease burden worldwide and the absence of a specific treatment? If they were to go ahead, Leroy and his team would also have to design the optimal market-entry strategy for the vaccine, including decisions on the countries to choose for the launch and the pricing. Leroy knew that the company had embarked on a strategy that was bold and brave, but also potentially high risk. He was concerned by the opportunity costs incurred, but at the same time, had not given up the hope that Sanofi's dengue vaccine would one day play a major role in public health.

Company Background

Sanofi's History

While its earliest roots dated back to 1718 when a family of pharmacists founded the Laboratoires Midy, which Sanofi later acquired, Sanofi itself as a company name appeared only in 1973. That year, Jean-François Dehecq established Sanofi Group, a corporate subsidiary of the French state-owned Elf Aquitaine oil company.[4] Dehecq grew the company with a vision to create a national industrial giant. His insistence on keeping Sanofi French drove the company's future string of acquisitions. In his first major acquisition in 1980, Dehecq acquired Clin Midy, a manufacturer of pharmaceuticals, veterinary, chemical, medical-surgical, and food products. This action significantly increased Sanofi's research and development budget and expanded the company's size by 50%.[5] In 1999, gradually moving away from its parent company Elf Aquitaine, Sanofi merged with Synthélabo, propelling the newly formed group to a position in the world's top-20 drug companies by size. Meanwhile, the pharmaceutical groups Rhône-Poulenc Rorer and Hoechst Marion Roussel had taken shape under their own respective mergers and, in 1999, combined to create Aventis, a Franco-German pharmaceutical group. Sanofi-Synthélabo, in turn, acquired Aventis in 2004, emerging as Sanofi-Aventis. Its vaccine subsidiary, Sanofi Pasteur, was formed that same year. In 2006, Dehecq stepped down as head of the company[6] (see **Exhibit 1** for an overview of Sanofi's history).

Chris Viehbacher was appointed as CEO on December 1, 2008.[7] A German-Canadian citizen, Viehbacher was an accountant by training and had managed the French and U.S. subsidiaries of British competitor GlaxoSmithKline before being passed over for the top job there. At Sanofi, Viehbacher's program of change, dubbed "Transforming," sought to reduce R&D and labor costs ahead of a foreseen loss of patent rights on drugs in 2012–2013, the so-called "patent cliff." Mindful of the temporary nature of patents, the industry's traditional revenue stream, Viehbacher broadened the company's focus from producing the greatest number of new, patentable molecules in R&D toward meeting patients' health needs. He halted the development of 30 out of 65 pharmaceutical products and encouraged external partnerships. By 2009, Sanofi reported a record net income of $7.5 billion, up by 16.9% from 2008[8] (see **Exhibit 2** for Sanofi key financial data). Viehbacher also led the acquisitions of 33 companies in 2009 alone, expanding Sanofi's portfolio of biotechnology, generics, public health, and animal health. For example, in line with Sanofi's focus on emerging markets, Sanofi's vaccines

division, Sanofi Pasteur, bought a majority stake in India's Shantha Biotechnics, gaining a portfolio of new vaccines under development. The next year, the company also acquired VaxDesign, a firm based in Orlando, Florida, which designed systems to predict human responses to vaccines in an attempt to accelerate vaccine development and better predict success in clinical trials. On May 6, 2011, Sanofi-Aventis simplified its name to Sanofi.[9]

By the end of 2011, Sanofi operated in more than 100 sites in 40 countries and employed more than 110,000 people. The company reported a slight decrease in net income due to competition from generic drugs, $7.3 billion on revenues of $45.5 billion.[10] About 32% of these revenues were generated in emerging markets, the group's largest geographic market. As a holding company headquartered in Paris, Sanofi was organized around three major activities: pharmaceuticals, vaccines, and animal health.

The Sanofi Pasteur Vaccine Division

Sanofi enjoyed a long tradition of developing vaccines, tracing its origins back to the achievements of the French chemist and microbiologist Louis Pasteur; French physicians Marcel, Charles, and Alain Mérieux; Canada's public health pioneer John FitzGerald; and New York bacteriologist Dr. Richard Slee (see **Exhibit 3a** for details on the history of vaccine development and **Exhibit 3b** for a typical vaccine development cycle). Although each followed his own path, they shared one goal: protecting humanity from infectious diseases. Leroy commented, "The mission of Sanofi Pasteur is to focus on preventing infectious diseases wherever we can, the same way Institut Mérieux, for example, helped immunize 90 million people over nine months in 1974, warding off an epidemic of meningococcal meningitis in Brazil."

Olivier Charmeil was appointed as executive vice president of the vaccine division in January 2011. A former banker, Charmeil had held various operational positions within the group, gaining an extensive knowledge of emerging markets, especially in Asia Pacific and China. By the end of 2011, Sanofi Pasteur reported $4.5 billion in sales. It employed over 12,000 people. With an output of over 1 billion vaccine doses that year, the company estimated that it had protected 500 million people from diseases worldwide. Following its parent company's global focus, Sanofi Pasteur had a strong presence in emerging countries, through both private markets and publicly funded channels such as UNICEF and the Global Alliance for Vaccines and Immunization (GAVI).

Headquartered in Lyon, Sanofi Pasteur also operated in 14 production and R&D sites worldwide. This geographical spread attested to its significant level of investment in recent years, including in new research facilities in Toronto, Canada; influenza vaccine facilities in Shenzhen, China, and Ocoyoacac, Mexico; bulk and filling facilities in Swiftwater, Pennsylvania, in the U.S., and Val de Reuil, France; and a bacteriological bulk facility in Marcy l'Etoile, France.

Sanofi Pasteur's product range was divided into five categories of vaccines for about 20 bacterial and viral diseases. Influenza vaccines protected against both pandemic and seasonal viruses and enjoyed rising global demand, due in part to increased awareness of the disease and government support for immunization. The pediatric combination and polio vaccines were tuned to varying public immunization requirements. Adult and adolescent booster vaccines complemented childhood immunizations against pertussis (whooping cough), as well as diphtheria and tetanus. Vaccines against bacterial meningitis and pneumonias had been launched in the Middle East and Latin America in the previous two years. Sanofi Pasteur also produced vaccines that protected travelers against illnesses endemic to their destinations, including yellow fever, cholera, and hepatitis A.

In addition to these existing products, the Sanofi Pasteur R&D portfolio contained 13 vaccines under various stages of development and testing. Five of them were new antibody or vaccine products, while the remaining eight were improvements of existing vaccines (see **Exhibit 4** for Sanofi's R&D portfolio).

The Vaccine Market and Its Competitive Environment

Although the vaccine market only made up approximately 2% of the world pharmaceutical products market (an estimated $850 billion for the overall market in 2011), analysts estimated that its growth would exceed out of pharmaceuticals. Vaccines were expected to grow at a compound annual rate of 8.9% from 2011 to 2016, as opposed to 6.2% for pharmaceuticals (see **Exhibit 5** for more details on the world vaccine market). Factors driving the growth of vaccines included demographic, technological, and political issues, among others. For example, a growing number of countries were seeking to vaccinate their population against an increasing range of diseases.

Vaccines were considered to be "cost effective," in that every dollar spent on immunization was estimated to avert $7–$20 in healthcare costs.[11] In addition to healthcare benefits, vaccination also revealed benefits that were not previously accounted for, such as potential effects on outbreak control spending, income from tourism, foreign direct investment flows, and long-term economic productivity.[12] Vaccines were usually less vulnerable to patent expirations and generics, as they required intensive know-how and technology, and production processes were difficult to standardize and copy. Some observers, however, reported that vaccines' profitability was lower in comparison to other pharmaceutical products; they argued that the pricing power of large purchasers such as governments and the high cost of fixed investments depressed margins.[13] Vaccines were also seen to be more likely to interfere with the spread of disease than drugs, thus reducing demand for the product.[14]

Vaccine manufacturers were conventionally divided into two groups: the multinational firms based in the U.S. and Europe, and the emerging suppliers based in developing countries. The first were highly concentrated. Five major players—Sanofi Pasteur, GlaxoSmithKline (GSK), Merck, Pfizer, and Novartis—dominated the global vaccine market, accounting for 82.2% of an estimated $19.8 billion in sales in 2011 (see **Exhibit 6** for data on the major vaccine manufacturers). Sanofi Pasteur led vaccines sales in emerging countries, with over 32% of vaccine revenues originating from emerging markets; in contrast, runner-up GSK derived 23% of its vaccine sales from those countries. Charmeil described Sanofi's position:

> We are the biggest company in emerging markets today. We have been in emerging markets for decades; we were the first foreign company into China in 1982, so we have a lot of depth and expertise in there. We sell more doses to emerging markets than we do to the United States, or in Europe. We try to be a local company wherever we are. We don't consider these regions as exports.

The emerging suppliers were a more diverse group, which included both traditional state-owned firms devoted to supplying national programs with basic vaccines and privately owned manufacturers. They traditionally sold older, less complex vaccines in high-volume, low-margin markets, focusing on exploiting cost advantages rather than innovation.[15]

On the demand side, there were three major customer segments for vaccines. By far the largest, the public or government market, negotiated vaccine prices with manufacturers for use in national or regional vaccination programs. In the public sector, governments were sometimes able to obtain

prices 50% to 60% below private-sector rates.[16] The second segment, the private sector, referred to vaccines that were distributed for use with individual consumers. In developing markets, many governments lacked the resources to meet their country's healthcare needs; a high portion of costs was paid out of pocket by patients.[17] Some experts reported that there was a shift from public to private markets for vaccines due to greater accessibility, a higher perceived quality of services, and the continuity of care offered.[18] Finally, the travel vaccines market targeted travelers from industrialized countries who required specific vaccinations for trips to developing countries with endemic diseases and amounted to $1.51 billion, 17.3% of the adult vaccine market in 2011.[19]

A number of stakeholders experienced success in accelerating the introduction of vaccines in poor countries. For instance, the Switzerland-based GAVI Alliance helped secure affordable prices for basic childhood vaccines.[20] Launched in 2000 by the Gates Foundation and WHO, GAVI contributed to the immunization of 370 million children and prevented 5.5 million deaths from hepatitis B, haemophilus influenza type B, measles, pertussis, pneumococcal disease, polio, rotavirus diarrhea, and yellow fever. Fifty-seven countries were eligible in 2012, based on their gross national income (GNI) per capita. The biggest beneficiaries (in order of decreasing value of vaccines received) were Pakistan, Ethiopia, Congo DRC, Bangladesh, Nigeria, Kenya, Ghana, Uganda, and the Republic of Sudan. Mostly funded by direct contributions (from donor governments, as well as personal and private-sector philanthropy), GAVI's total disbursements reached $690 million in 2011.[21]

In terms of coordination, WHO regional and country offices provided expert recommendations on vaccine use and appraisal of new vaccines. Each country then determined what their immunization needs were, applied for funding, and oversaw the implementation of their vaccination programs. GAVI provided funding for vaccine procurement, and UNICEF's supply division made the purchases. Countries were asked to start cofinancing as soon as they introduced new GAVI-supported vaccines and, depending on their level of GNI per capita, to make gradually increasing contributions. Competition that was open to all bidders who met the qualifications and contract performance requirements was the normal procurement method for contracts exceeding $250,000[22] (see **Exhibit 7** for data on GAVI).

Another stakeholder, the Pan American Health Organization (PAHO), also enjoyed international recognition as part of the United Nations system. PAHO had launched the Revolving Fund for Vaccine Procurement in 1979 as a procurement mechanism for essential vaccines, syringes, and other related supplies. Funded by member states in the Americas, the Revolving Fund managed the planning and consolidation of demand, negotiations with producers, placement of purchase orders, coordination with suppliers, and monitoring of shipments, as well as the financial aspects involving paying suppliers and billing countries. Through a system of bulk purchasing, the fund had secured a supply of 178 million WHO-prequalified vaccine doses in 2011, at a total purchase value of $405 million.[23] The Revolving Fund coordinated operationally with GAVI, so that GAVI-eligible countries in the Americas could have access to a predetermined set of new vaccines.[24]

Dengue, Also Known as Breakbone Fever

The Disease

Dengue fever was a viral infection transmitted by mosquitoes in tropical and subtropical regions of the world. The disease was endemic[b] in over 100 countries,[25] many of which were low- or middle-income countries, with the most severely affected regions being parts of the Americas, South and

[b] Endemic disease referred to a disease that was regularly or ordinarily occurring in a given region.

Southeast Asia, parts of Sub-Saharan Africa, and the Western Pacific (see **Exhibit 8** for maps of areas most at risk). Dengue had increased in urban and semi-urban areas since its identification in the 1950s, and had become a leading cause of death and hospitalization of children in endemic regions. WHO estimated that there were from 50 million to 100 million new dengue infections per year, though other estimates reached as high as 390 million infections. Around 500,000 children suffered from severe dengue and required hospitalization each year; 2.5% of those patients died.[26] Economically, the disease's burden on society included direct medical costs to the health system or individuals, nonmedical costs related to the treatment of the disease, and lost productivity (work or school days lost by the patient or family members as a consequence of the disease). In recent years, dengue outbreaks increased and started to affect new regions in Europe and in the United States.[27]

Four closely related strains, or serotypes, of the dengue virus were known to cause the disease: DEN-1, DEN-2, DEN-3, and DEN-4. The prevalence of these strains traditionally varied geographically, but co-circulation of all four serotypes was common in highly endemic areas. A person's recovery from infection by one serotype provided lifelong immunity against that particular serotype. Cross-immunity to the other serotypes after recovery was only partial and temporary. A subsequent infection by another dengue serotype was more likely to lead to an even more severe form of the fever.[28]

The main vector, or carrier, of these strains was the female *Aedes aegypti* mosquito. It acquired the virus by biting an infected person and transmitted dengue with subsequent bites. After 8–12 days, the mosquito incorporated the virus into its system and was able to transmit it without feeding on any new infected human. The lifespan of an adult *Aedes aegypti* was two to four weeks. The mosquito traveled within a range of only 400 meters, meaning that human movement, not mosquitoes', brought dengue infections into new places and communities. Infections were more frequent outdoors and in the daytime, although the mosquito fed at any time of the day.[29]

In infected individuals, flulike symptoms appeared 4–10 days after infection and included severe headaches, pain behind the eyes, nausea, vomiting, swollen glands, muscle and joint pains (hence the nickname "breakbone fever"), and rashes. Severe dengue (known as dengue hemorrhagic fever) could in some cases follow 3–7 days after the first symptoms. Its complications included severe abdominal pain, persistent vomiting, rapid breathing, bleeding gums, blood in vomit, fatigue, and restlessness, as the patient experienced plasma leaking, respiratory distress, fluid accumulation, severe bleeding, and organ impairment.[30] Dengue hemorrhagic fever was a rare but severe, often fatal complication of dengue fever.[31] There was no known drug or treatment for dengue; only proper hydration and rest could alleviate the symptoms. For severe dengue, medical care that maintained fluid circulation in the first 24–48 hours was critical to saving lives.

Other measures to contain the disease relied on vector control, reducing the mosquito population and minimizing mosquito-to-human contact.[32] Vector control attempted to manipulate the surrounding environment to reduce the number of habitats favorable to mosquitoes, for example, by installing mosquito nets.[33] Chemical insecticides were also used in some instances to kill adult and larval mosquitoes,[34] while mosquito predators such as fish and small crustaceans or competing mosquito species were introduced in others.[35] As Leroy reflected, "Dengue is so big and painful for public health that any single activity to try to develop a solution is extremely well received."

Vaccine Candidates

Pharmaceutical companies had been working on a dengue vaccine for decades. Researchers discovered the four dengue serotypes between 1944 and 1956, and they developed a first dengue

vaccine in 1944–1945, which used a live attenuated virus to target the DEN-1 substrain. By the 1980s, teams at several institutes and universities supported the development of a tetravalent, live, attenuated vaccine able to target all four dengue serotypes. Progress toward a marketable vaccine stalled, however. There were many hurdles to the development of a successful vaccine. These included technical challenges surrounding development of a vaccine that protected against all four strains of dengue, limited understanding of how the disease behaved and how the virus interacted with the immune system, as well as lack of laboratory animal models available to test immune responses (because dengue virus did not naturally infect nonhuman species).[36]

Sanofi Pasteur began developing a live, attenuated vaccine in 1994. In the same year, it became the first pharmaceutical company to invest in the R&D of a dengue vaccine when it partnered with Mahidol University in Bangkok, Thailand, which had developed the original tetravalent candidate. Sanofi Pasteur obtained proof of concept for a tetravalent, two-dose and booster version in 2001, but the company had to abandon that candidate due to its highly adverse effects in the Phase I trials.

The company inherited further advances in the dengue vaccine from its 2004 acquisition of U.S. firm Acambis, which had been developing a recombinant vaccine technology[c] in its product pipeline. As a direct consequence of this acquisition, Sanofi Pasteur thus produced a second-generation vaccine, hoping to overcome previous difficulties. *In vitro* and *in vivo* preclinical studies (conducted outside and within a living organism) showed promising results. Sanofi Pasteur's dengue vaccine product entered Phase I clinical trials in 2004. In 2007, positive results were obtained in Phase II clinical studies. In 2009, Sanofi Pasteur dengue vaccine entered a pediatric clinical efficacy study in Thailand (Phase IIb). In June 2010, the U.S. Food and Drug Administration (FDA) granted fast-track status to the dengue candidate[d] (see **Exhibit 9a** for a timeline of the dengue vaccine development).

According to the company, Sanofi Pasteur was ahead of the competition in dengue vaccine development. Industry experts estimated that other vaccines could come into production between 2017 and 2021 if successfully developed and approved by regulators. GSK was conducting Phase II trials with the aim of producing a single-dose vaccine in conjunction with the Walter Reed Army Institute of Research in the U.S. The company had conducted several clinical studies in the U.S., Puerto Rico, and Thailand, and had partnered with Fiocruz, a Brazilian foundation, for the development and manufacturing of a dengue vaccine in Brazil.[37] Inviragen, working with the Centers for Disease Control and Prevention, was also a few years behind with a candidate vaccine in Phase II clinical testing. Dr. Dan Stinchcomb, Inviragen's CEO, commented:

> Sanofi Pasteur had the leading dengue vaccine in clinical testing for several years. Unlike the Sanofi vaccine, which uses a yellow fever backbone, Inviragen's vaccine was engineered with a dengue-2 backbone. As a result, our vaccine has the potential to generate more potent immune responses. Also unlike the Sanofi vaccine, which is delivered in three doses that take a full year to administer, DENVax is delivered in only two doses in three months.[38]

Four other companies had vaccine candidates in Phase I. In addition, there was a large variety of candidates in preclinical development, which were based on diverse technologies, ensuring a continued influx of innovation into the development pipeline[39] (see **Exhibit 9b** for details on the dengue vaccine candidates). Michael Watson, vice president for vaccine policy advocacy at Sanofi

[c] Recombinant vaccines were engineered viruses or bacteria into which harmless genetic material and other disease-causing organisms were inserted.

[d] Fast track was a process designed to facilitate the development and expedite the review of drugs to treat serious conditions and fill an unmet medical need. The purpose was to get important new drugs to patients earlier.

Pasteur, commented, "Realistically I believe we are 10 years ahead of our competitors. If someone managed to produce large volumes of a single-dose vaccine, which conferred efficient protection against the four substrains, then it would be a huge threat for us. But right now, the other candidates are all in the early stages of development."

Resources Dedicated to the Project

Sanofi had dedicated significant resources toward the vaccine and made an unusual decision from the start: to develop the vaccine, set up the industrial capacity, and prepare the market-entry launch in parallel (and not in sequence, as the company and its competitors used to do). Viehbacher explained:

> I became CEO in December 2008. On my first day, there were these documents sitting on my desk, asking for a €300 million investment [$398 million] to build a new factory for the dengue vaccine, even though we had not even finished clinical trials yet. The attached memo said: 50% probability of success of the vaccine candidate in development. I said, "Wait a minute, guys; I'm not signing this thing unless you tell me we have at least a 70% probability of success." But this was impossible to know for sure at that stage, of course. In the end, it was a personal decision. The nature of vaccines is such that generally you have a better feeling for the success of a vaccine than you do for a new drug. There was a risk, but I signed.

In May 2009, Sanofi Pasteur broke ground on a dengue vaccine facility without knowing whether the Phase IIb clinical trials would be positive or not. Sanofi Pasteur converted an existing chemical site to a new vaccine manufacturing center in Neuville-sur-Saône, France. The factory was expected to produce more than 100 million commercial doses a year, employ 200 people, and be operational as early as 2015. It was the largest investment ever made in Sanofi's global vaccines industrial network.

The simultaneous development of the production site in parallel to the vaccine was one of the key conditions for being ready to supply the market the day after approval. Leroy explained, "If we hadn't planned ahead, we might have had to wait another five years after conclusion of the clinical trials before we could complete the facility to produce the vaccine. In the vaccine industry, our industrial capacity is our main tool to conquer the market and get public health impact. The advance in terms of industrial capacity should be a very strong asset in our marketing strategy." Charmeil added, "Dengue is a public health emergency. There is no treatment for dengue today; the people who die from it tend to be children. If you have a public health emergency, to spend five years to build a factory would be really unethical."

The move was, however, very risky. "It is a gamble. They have to invest before knowing what will be the final profile of the product," said an analyst.[40] The investment cost was estimated at more than $1.5 billion.[41] Viehbacher commented, "That's the nature of our business. You've got to take these big bets. We increased our level of risk. If we fail, our hopes will be dashed."

In order to mobilize staff; provide a common vision and strategy; and secure execution, time, and budget, the company also developed an innovative organizational model in mid-2011. The Dengue Company was a core group of 500 Sanofi Pasteur employees from all functions dedicated to dengue vaccine development, production, and marketing. Other Sanofi Pasteur and Sanofi employees assisted Dengue Company on an ad hoc basis. Leroy was appointed as vice president in September 2011. Coming from a strong pharmacy and business administration background, Leroy had extensive knowledge of immunization needs and implementation of vaccination programs, especially in Latin America. The Dengue Company was fully integrated and transversal. It was the first time Sanofi had created such a separate internal structure for a vaccine. Leroy explained:

> We have three horses: R&D, industrial operations, and commercial operations; we have to make sure that the three horses are running at the same speed. Otherwise there is a risk of delay. We need to consolidate the risks to be as robust as possible. The level of visibility of dengue in the public health agenda is extremely high. The potential for a dengue vaccine will be extremely visible for the company in terms of image and reputation.

Roberto Pucci, Sanofi executive vice president of human resources (HR), commented, "We needed to structure the organization to function well together. We needed a way to create and focus the interest and motivation from the different pockets of the organization. From an organizational point of view, you need to have an alignment across the entire organization to create a structure with the same sort of objectives, KPI [key performance indicator], and reward systems."

But Watson pointed out, "The weaknesses related to this model are that you have to be careful that it doesn't suck up the best talent, and that it doesn't distract people from other important priorities within the business. In emphasizing the importance of anything, you have to be careful not to deemphasize the importance of other things." Charmeil added, "One of the crucial things is how much of the company you keep autonomous in some areas and how much you integrate."

Potential Market, Projected Production Capacity, and Manufacturing Cost

Potential market The Pediatric Dengue Vaccine Initiative (PDVI) estimated the potential vaccine demand in dengue-endemic countries and among travelers at about 3.5 billion dengue vaccine doses in the first five years after introduction, with more than 75% delivered in the public sector. The study identified 20 potential early-adopter countries (which included, among others, Brazil, Malaysia, Philippines, and Thailand), in which about 1.4 billion doses would be needed for the same approach. The Dengue Vaccine Initiative estimated that this upper limit was not likely to be demanded because, in practice, fewer countries might introduce the vaccine, owing to lack of funds and competing priorities. Furthermore, the catch-up vaccination that would need to accompany routine immunization programs[e] might possibly have been overestimated. For the private sector, covering 10% of children and 30% of adults, researchers estimated that 664 million doses would be required in the first five years after introduction. Similarly, in nonendemic countries, travelers could potentially use an estimated 89 million vaccine doses.[42] The Dengue Vaccine Initiative reported that it was likely that the first adopters of dengue vaccines would be countries in which vaccine clinical trials were being conducted. It estimated that there would be important markets in both the public and private sectors, with private-sector introduction likely preceding public-sector adoption[43] (see **Exhibit 10** for more details on the vaccine demand in dengue-endemic countries).

Typically, countries would face a very high initial rollout cost, spread over a three- to five-year introduction campaign, followed by the lower long-term maintenance cost for vaccinating newborns each year as part of the immunization schedule. The total rollout cost would depend on whether the vaccine was introduced only in high-risk urban areas or in the entire country, and whether it would cover only a section of the population (children or adults). A survey projected that for the first five years of use in Brazil, considering the entire endemic area and all ages, approximately 299 million doses would be needed at a vaccine purchase cost estimated at between $1.5 billion and $4.5 billion.[44]

[e] Vaccines were administered according to several schedules. Routine immunizations targeted babies and infants, starting at birth, with a standard set of vaccines. Vaccines sometimes required multiple doses, scheduled at intervals of years or months between administrations. Should adults and older children miss these initial shots, they could still obtain the same vaccinations on a catch-up schedule.

Opinion was therefore divided on whether everyone could and should get vaccinated. Charmeil commented, "You got half the world's population at risk for dengue. That's 3 billion people; are you going to vaccinate 3 billion people? Probably not. How are you going to define who is the risk population? What are the economics around that, and who should really get vaccinated?"

Projected production capacity Sanofi Pasteur's dengue vaccine was expected to be approved and available for distribution by 2015.[45] Sanofi Pasteur decided that the annual plant capacity would be limited to 100 million doses, which would be sufficient to vaccinate 33 million people, assuming a three-dose regimen and no wastage. An industry expert noted, "Unless someone pops up with something fantastic, Sanofi Pasteur will be the sole producer for a few years. Capacity will be limited and they will not be able to reach everyone."[46]

Manufacturing cost Vaccine production costs were highly volume sensitive, with per-dose costs dropping significantly as production volume increased. The majority of costs were fixed (60%) or semi-fixed (25%), regardless of volume.[f] Variable costs such as raw materials and packaging represented only 15% of the total. Viehbacher commented:

> Biological manufacturing is quite interesting. This is an artisanal process, growing viruses, getting the humidity and the temperature right. To give you an idea, when we were making the pandemic flu vaccine, we needed one egg to get one dose. Three months later, we could get three doses out of an egg, which is a 200% improvement in yield.

No Smiley Face

Conducted in parallel with the Phase III clinical trials, Sanofi's current Phase IIb testing was designed to check the vaccine's efficacy in the Ratchaburi province of Thailand. The study enrolled 4,002 children aged 4 to 11, with the approval of the Thai Ministry of Public Health and the collaboration of the local Mahidol University. Doctors administered three doses of the Sanofi Pasteur dengue vaccine with six months between each shot. In case of good results, the company, which anticipated a rate of overall efficacy of approximately 70%, was planning to file for early marketing approval in some countries, such as Australia, Malaysia, Mexico, Singapore, and Thailand, hoping for a regulatory green light in 2014 and commercial launch in early 2015.[47]

However, the results that Leroy had received and kept reviewing had found effective protection against only three of the four substrains. The full analysis of vaccine efficacy per serotype showed vaccine efficacy of 61.2% against DEN-1, 81.9% against DEN-3, and 90% against DEN-4. One of the dengue virus types (DEN-2) eluded the vaccine; efficacy was statistically not superior to 0.[48] The overall efficacy rate, which therefore had dropped to 30.2%, came as a complete surprise.

The Dengue Company's top executives jammed into the conference room to discuss the clinical trials and agree on a strategy. Lang opened the discussion:

> I think it's a surprise not only for us, but also for the whole scientific community. The vaccine induced satisfactory antibody responses by the gold standard assay[g] against each of

[f] These costs usually included research and development, quality control and quality assurance, selling and distribution overhead, and the construction and maintenance of production facilities.

[g] The gold standard assay referred to the biological assay by which the company evaluated the quality and quantity of antibodies in the vaccine-induced immune response. In this case, Sanofi Pasteur used the World Health Organization–validated assay, whose results were thought to be associated with protection (although no strict assay correlate of protection existed).

> the dengue viruses. However, it didn't provide protection against one serotype. Our assumptions on the causality between antibodies measured by this assay and protection for the four serotypes were false. The disease caused by four viruses is far more complex than what we thought. On the other hand, there were 50 years of vaccine safety failure before we ended up with this candidate. We obtained a safe and immunogenic vaccine for the four serotypes and protection against three out of four. It's the first time we reached that result.

Leroy knew that it would not be easy to find a satisfactory explanation of these results, as any one or more of the four key factors influencing vaccine-induced immunity could have played a role in limiting the candidate's efficacy: the circulating viruses in the region at the time of the study, the vaccine candidate itself, the mosquito vector, and the host's pre-immune status. Lang added:

> We knew, based on prior epidemiological studies, when selecting the Phase IIb trial unique site that we ran these trials in one of the world's dengue "hottest places." Maybe the infectivity[h] of this Thai virus was too high. Maybe the vaccine potency was a bit low. Maybe the Thai mosquito vector had some unique capability. Maybe we can explain the results by a specificity of this selected Thai trial population. We need to look into all of the possibilities very carefully, but as the explanation is likely to be multifactorial, this will not be easy to investigate.

The Road Ahead

Wait for Results of Large Phase III Trials or Start New Vaccine Development

Already the first reactions from industry experts started to appear in the press, several of them considering these conclusions as extremely perplexing and disappointing. An analyst noted, "This is a very sobering outcome. Further experimentation is going to have to be done in order to understand what happened."[49] Reading the latest news stories, Claude Spieser, senior VP of global industrial operations, immediately reacted, "We have to continue to work. I know it's difficult and demanding to be the first ones, but I am very confident that we are going to master it." Lang added, "We need to wait for the results of the two ongoing, large Phase III efficacy trials [30 sites in 10 countries with over 30,000 subjects] to have a better understanding of the vaccine before making any hasty decisions. Perhaps in another location and with a larger sample, we will get better results and can figure out what went wrong in this Ratchaburi site, Thailand."

Leroy was wondering whether the team was right. Considering the lack of existing treatment and the heavy cost of the disease in endemic countries, a dengue vaccine could potentially be a huge success for the Dengue Company in terms of public health objectives. A first-mover advantage was crucial in the vaccine industry. Watson recalled how the MSD Gardasil vaccine entered the market first and made spectacular use of its advantage; the vaccine raked in global sales of over $2 billion in its first full year on the market. Could Sanofi Pasteur have a new success story? Besides, the company had already invested large amounts in R&D and infrastructure. The risk was high but it might be worth it. Continuing to go ahead with the larger trials and hoping these would yield better results was perhaps the best solution. If these results were at least slightly better, this might be enough to get the vaccine out on the market. Lang commented, "At a certain point, you have to go to the market. It doesn't mean it's the gold standard. There's always room for improvement. What do people have to offer against dengue as an alternative? Nothing! We should be proud."

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[h] The infectivity of a virus referred to the tendency to spread rapidly from host to host.

Alternatively, Charmeil was wondering whether he should start a new dengue vaccine development. Results of larger Phase III trials were difficult to predict and were beyond the control of Sanofi, bringing uncertainty to the future of the product and its approval by national regulatory authorities. If further tests confirmed such a low efficacy rate, would the vaccine even obtain licensure? A new vaccine could fail at any stage of the development process. Should Leroy stop to invest in the current program and retrofit the factory before proceeding with further experimentation and generating additional costs? Spieser noted, "We could probably reuse the factory for something else, but we probably would have to spend another €50 million to €100 million [$69 million to $139 million]." Spieser had to admit, "Sometimes, it happens. You dismantle and divest for one-tenth of the value something you didn't have the opportunity to operate. That is the real risk in our business." Was this solution under consideration? Leroy had to move forward, but in which direction?

Go-to-Market Strategy and Vaccine Pricing

High-income countries versus low- and middle-income countries If the company decided to continue its efforts toward a dengue vaccine, Leroy and his team had to make decisions on how the product should be marketed.

Leroy was wondering whether the Dengue team should first market the product as a "travelers" vaccine in high-income markets to quickly recover a portion of the R&D costs (which meant a high-priced vaccine and relatively low volume), as had been the most common industry practice so far. Considering the increase in outbound travel and improved awareness about vaccine-preventable diseases, the travel market for dengue vaccines in developed countries appeared to be small but viable. According to industry experts, Sanofi could potentially target these customers, but the volume sold would probably constitute a small proportion of production (potentially 10%).[50]

Alternatively, should Sanofi Pasteur go against the traditional "first north, then south" way and launch the product at a low price in developing-country markets, which often had smaller health budgets but higher-volume needs, and then launch a travelers' vaccine at a later stage? Given the dengue geographical incidence (65% of persons at risk were in GAVI-eligible countries), some observers reported that Sanofi would be subject to substantial community pressure to sell most of its vaccine in lower- and middle-income countries. Sanofi already had long experience in developing-country markets, public and private, and sold in large volumes to UNICEF. Sanofi Pasteur was a key member of several important global vaccine consortiums, including the International Federation of Pharmaceutical Manufacturers and the Pediatric Dengue Vaccine Initiative. Sanofi was used to modest profits from sales in developing countries; this constituted an integral part of its business model. Sanofi also agreed to provide the new vaccines to GAVI at significant discounts for use in the poorest countries. Viehbacher commented on the need to make a substantive contribution to global health:

> Are we simply a supplier of vaccines and pills to the healthcare system, or do we see ourselves as being an active supplier in public health? Dengue offers this opportunity to show, from a broader perspective, that we are not just about healthcare in rich countries. I want us to be an actor in public health. This isn't just me being a humanitarian. I see a very clear business proposition there. To me, an emerging market is as important as a U.S. market.

Selecting emerging markets first would bring additional questions in terms of go-to-market strategies. For instance, should the introduction of dengue vaccine be in low-income countries, supported by GAVI, or in middle-income countries, not eligible for heavily discounted prices but where an estimated 70% of the world's poor—or almost a billion people—were living?[51] Should

Sanofi select a larger market first, rather than a smaller country? Should the introduction be nationwide, given the burden of the epidemics, or should the vaccine be rolled out in a few provinces first to demonstrate its effectiveness, determine the best strategies for implementation, and work out logistical challenges?

The final alternative was an in-between option, pursuing a hybrid approach and marketing the product in high-income and low-income countries simultaneously. Was this even possible?

Pricing Leroy also had to make decisions on whether Sanofi Pasteur should consider offering products at completely different price points and, if so, what pricing strategy to adopt. The price of a vaccine typically depended on the demand, the size of the market, and the immunization strategy that was selected by national authorities. Several other factors were considered: (1) the country's ability to pay for vaccines; (2) the price that the country was willing to pay; (3) the vaccine manufacturers' ability to sustainably provide a vaccine at the price that a country could afford and/or was willing to pay; and (4) whether mechanisms were in place that enabled countries that couldn't afford to pay full price to gain access to the vaccine.[52]

For the middle classes of Latin America and Asia, for example, an out-of-pocket purchase of a dengue vaccine seemed affordable. Yet, dengue took its biggest toll among the poor. Getting the vaccines to them would require the elaboration of national public immunization programs, the involvement of international agencies such as GAVI, and the introduction of Ramsey pricing (also known as "differential pricing" or "tiered pricing").[i] Four different tiered-price policies were usually adopted by manufacturers: (1) pricing in the country of manufacture, taking into account the local regulations and discounting system, such as a commission to the distributors or chemists; (2) differential pricing for export in the private market (again taking into account the local commission structure); (3) pricing for middle-income countries; and (4) pricing for GAVI-eligible countries.[53]

For the public sector, pricing of dengue vaccines was unlikely to be determined by the free market. It would instead be determined through negotiation with key national governments, which would then set a benchmark for other countries to follow, as had happened with GSK's pneumococcal vaccine. According to an eight-country survey of policymakers and opinion leaders (which included representatives from Brazil, Colombia, India, Mexico, Nicaragua, Sri Lanka, Thailand, and Vietnam), the price of dengue vaccines to the public sector would be a major determinant of whether or not governments would introduce the vaccine. A Thai official, for example, suggested that a price of less than $10 a dose would be acceptable, while the maximum acceptable price given by Mexican representatives ranged from less than $10 to $15 per dose. A university health economist in Colombia felt that full introduction would take a long time unless the vaccine cost no more than $5 per dose. In Vietnam, one Ministry of Health official believed that $5 per dose was much too expensive, while another gave a preferred price of $1 per dose.[54]

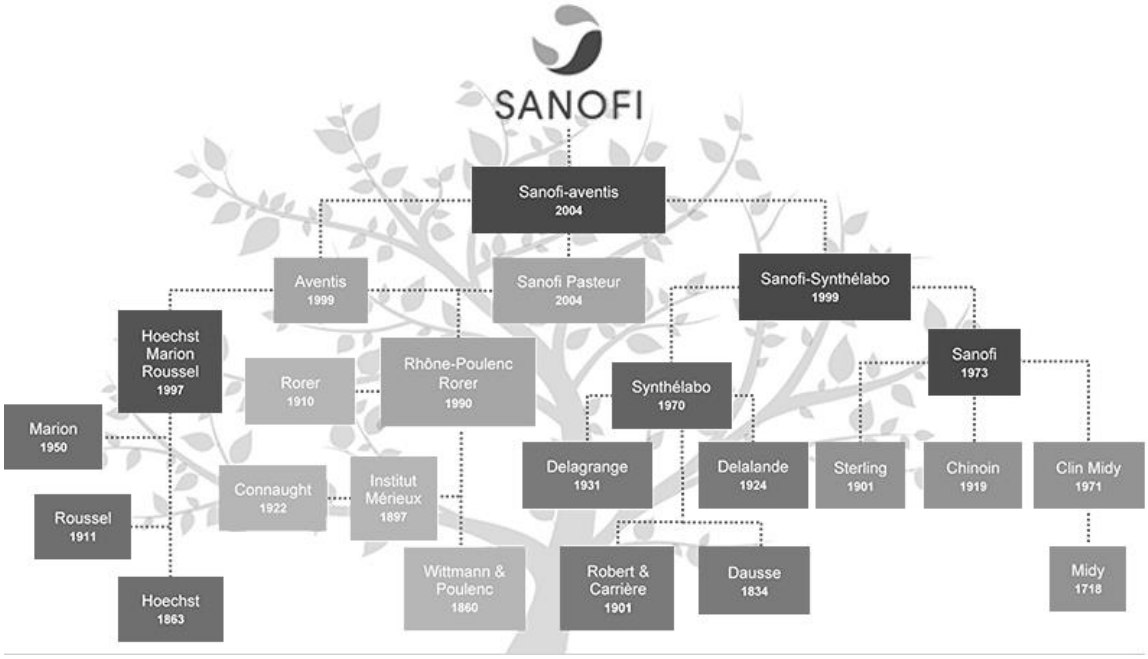
An industry expert proposed a totally different range: "I would expect that for middle-income countries, Sanofi Pasteur would be looking at prices similar to those of other new vaccines—for example, HPV, pneumococcal, and rotavirus vaccines—which sell for $15 to $70 per course in countries like Brazil, South Africa, Venezuela, and Thailand."

[i] According to WHO, differential pricing, also known as tiered pricing, meant that different classes of buyers were charged different prices for the same product. In the context of vaccines, low-income countries were charged a reduced price compared to the open market rate through bulk procurement systems established by the United Nations Children's Fund (UNICEF) and the Pan American Health Organization (PAHO). The idea behind differential pricing was to reduce financial barriers to vaccine access for low-income countries while providing manufacturers with a profitable market in richer markets so that they would have an incentive to invest in sufficient production capacity and new product research and development.

Should the vaccine be priced following these recommendations or should it be substantially higher than traditional vaccines? Past experience with Wyeth's pneumococcal vaccine Prevnar and Merck's HPV vaccine Gardasil, each of which brought in more than $2.8 billion in sales in 2008 due to very high prices (over $305 for a three-dose course of Gardasil), shattered the notion of vaccines as low-margin commodities (see **Exhibit 11** for data on vaccine pricing). Could Sanofi be similarly successful with a high-price policy, or would this move potentially limit demand for the product? Viehbacher reflected, "Every country is going to say, 'Well, I shouldn't pay anything.' What is the equity in there? What is the cost of a dengue vaccine versus, for instance, an AIDS treatment? What is the cost of dengue vaccine versus an HPV vaccine, or a polio vaccine? This is difficult."

Leroy was listening to the team's ideas and rereading the trial documentation. He needed to decide whether to go ahead with the vaccine trials and production, and if so, he had to develop a strategic plan for how to price and deliver the vaccine for a rapid rollout. Leroy knew the time had come to make a recommendation. Carefully weighing the pros and cons of each option, he had made his decision. He knew what his suggestion would be for where to go next.

Exhibit 1 Sanofi's History



Source: Company documents.

Exhibit 2 Sanofi Key Financial Results

a) Sanofi Key Statistics ($ million, 2008–2011)

For the Fiscal Period Ending	2011	2010	2009	2008
Total revenue	45,545	45,640	44,761	40,267
Net sales	43,376	43,402	42,687	38,522
Other revenues	2,168	2,238	2,074	1,745
Growth over prior year %	3.0%	9.0%	8.4%	(1.3%)
Gross profit	32,000	33,228	33,271	30,017
Margin %	70.3%	72.8%	74.3%	74.5%
EBITDA	16,705	17,837	17,869	14,880
Margin %	36.7%	39.1%	39.9%	37%
EBIT	10,050	11,579	11,375	8,746
Margin %	22.1%	25.4%	25.4%	21.7%
Net income	7,396	7,331	7,546	5,381
Margin %	16.2%	16.1%	16.9%	13.4%
Diluted EPS excl. extra items	5.57	5.61	5.78	4.11
Growth over prior year %	2.6%	3.7%	37.1%	(24.4%)

Source: Standard & Poor's, Compustat data via Capital IQ, accessed August 2013.

Exhibit 2 (continued)

Consolidated Net Sales by Business Segment ($ million, 2010–2011)

	2011[a]	2010[b]
Pharmaceuticals	36,232	35,637
Vaccines	4,507	5,106
Animal Health	2,637	2,659
Total	43,376	43,402

Source: Company documents.

[a] 1 EUR = 1.30 USD (as of Dec. 31, 2011). [b] 1 EUR = 1.34 USD (as of Dec. 31, 2010).

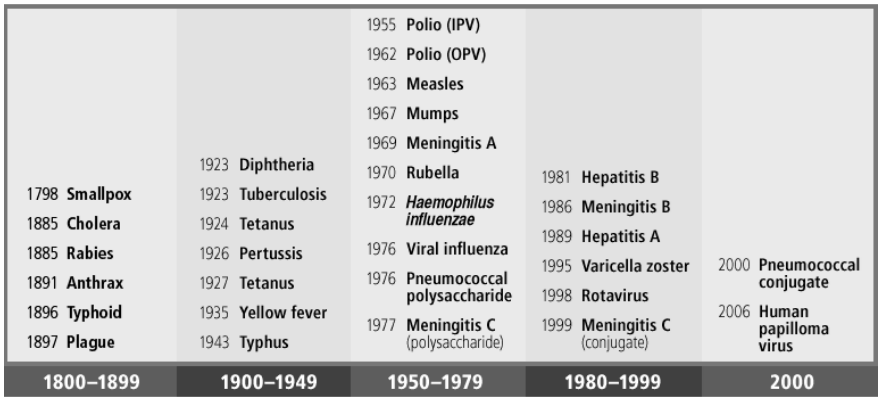
b) Vaccine Consolidated Net Sales by Geographic Region and by Product ($ million,[a] 2011)

	Western Europe	United States	Emerging Markets	Other Countries
Polio/Pertussis/Hib Vaccines	47	601	594	155
Influenza Vaccines	100	565	384	23
Meningitis/Pneumonia Vaccines	4	507	135	17
Adult Booster Vaccines	99	440	39	26
Travel & Other Endemics Vacc.	31	116	273	61
Other Vaccines	19	229	21	21
Total	300	2,458	1,446	303

Source: Company documents.

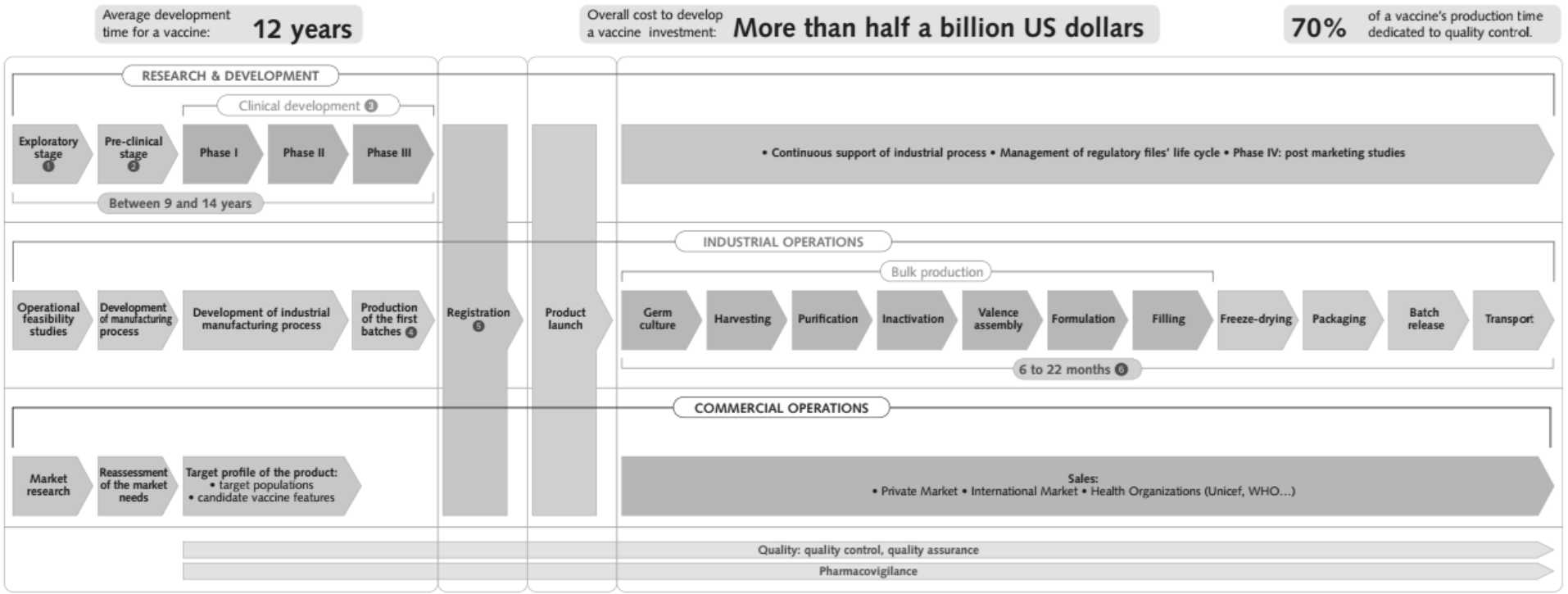
[a] 1 EUR = 1.30 US$ (as of Dec. 31, 2011).

Exhibit 3a Vaccine Development Timeline



Source: World Health Organization, "History of Vaccine Development," WHO Website, http://www.vaccine-safety-training.org/history-of-vaccine-development.html, accessed August 2013.

Exhibit 3b The Vaccine Development Cycle



Source: Company documents.

Notes: 1) **Exploratory stage: 2 to 4 years**. Identifying antigens to prevent or treat a disease.

2) **Pre-clinical stage: 1 to 2 years**. Assessing antigens' safety in animals and selecting the best candidate vaccine to continue the process.

3) **Clinical Development: 6 to 8 years**. Testing the candidate vaccine in humans. *Phase I*: Test of safety on 10 to 100 subjects. *Phase II*: evaluation of the immune response in 100 to 3,000 subjects. *Phase III*: Large-scale tests of the vaccine's efficacy and tolerance on 3,000 to 40,000 subjects.

4) The first batches were clinical batches and industrial batches of compliance.

5) **Registration: synthesis stage from 12 to 18 months**. All of the data that had been collected during the preceding stages were gathered in a file and submitted to the health authorities in order to obtain a marketing authorization. Though largely similar, regulatory procedures differed among countries and regions. A vaccine often had to earn approval for every market it wished to enter. To gain access to some markets, such as Brazil, it was also often required that some component of vaccine production, or even technology transfer leading to complete local vaccine production, would take place in the country.

6) The infectious germs were cultured, harvested, and purified. After formulation and freeze-drying (which stabilized the more fragile vaccines), the vaccines were put into vials and syringes, and then packed. When the manufacturing process was complete, the cold chain had to be constantly maintained during all stages, from distribution to vaccine administration to patients.

Exhibit 4 Sanofi Pasteur R&D Portfolio (as of end of 2011)

Phase I	Phase IIa	Phase IIb	Phase III	Submitted
Streptococcus pneumonia	Meningitis A, C, Y, W conj.		Quadracel *(DTP)*	Hexaxim *(DTP-HepB-Polio-Hib)*
Tuberculosis	Rabies VRVg		Dengue	
Rotavirus (shantha)	ACAM C. Diff *(Clostridium difficile Toxoid)*		Fluzone QIV *(influenza)*	
Pseudomonas aeruginosa			Vaxigrip QIV IM *(influenza)*	
			DTP-HepB-Polio-HIB Vaccine	

Source: Company documents.

Note: D = Diphteria; T = Tetanus; Hib = Haemophilus influenzae type B; HepB = Hepatitis B; P = Pertussis.

Exhibit 5 World Market for Pediatric and Adult Vaccines by Region (revenues in $ millions, 2007–2011)

Year	U.S.	North America & Carib.	South America	EU	Japan	India	China	Rest of World	Total
Pediatric Vaccines									
2007	2,718	245	505	2,329	621	466	543	338	7,765
2008	3,189	290	594	2,751	731	558	649	377	9,139
2009	3,739	340	709	3,245	860	667	773	412	10,745
2010	4,039	372	768	3,527	919	733	850	431	11,639
2011	3,849[a]	354	745	3,382	879	712	823	380	11,124
Adult Vaccines									
2007	2,738	246	508	2,347	626	469	548	340	7,822
2008	2,941	268	548	2,536	674	514	598	348	8,427
2009	3,543	323	672	3,074	814	631	733	390	10,180
2010	4,355	401	828	3,803	992	791	916	465	12,551
2011	3,021[b]	278	585	2,654	690	559	646	298	8,731

Source: Compiled by casewriters from Alison Sahoo, "Vaccines 2012," Kalorama Information Market Intelligence Report, September 2012, http://academic.marketresearch.com, accessed June 2013.

[a] 56% of the world market for vaccines in 2011.

[b] 44% of the world market for vaccines in 2011.

Exhibit 6 Major Vaccine Manufacturers

a) Major Manufacturers' Shares of the World Vaccine Market (2011)

Company	Market Share
GlaxoSmithKline	27.4%
Sanofi Pasteur	21.5%
Merck	19.6%
Novartis	7.7%
Pfizer	6.0%
Others	17.8%
Total	100%

Source: Alison Sahoo, "Vaccines 2012," Kalorama Information Market Intelligence Report, September 2012, http://academic.marketresearch.com, accessed June 2013.

Note: Others included Baxter Vaccines AG, Bavarian Nordic A/S, Crucell, Emergent BioSolutions, Green Cross Vaccine Company (Korea), Biotest, and the Merck-Sanofi Pasteur joint venture.

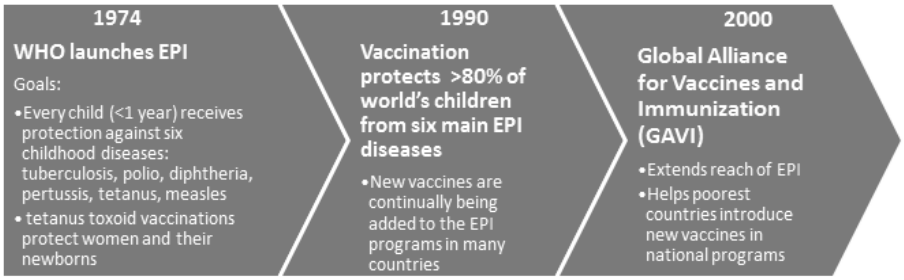
b) Top-selling Vaccines (2011)

Name	Type	2011 Sales	Developer/ Sponsor
Prevnar 13®/Prevenar 13	Pneumococcal 13-valent conjugate vaccine (diphtheria CRM197 protein)	$ 3.7 billion	Pfizer
PENTAct-HIB	Hemophilus influenzae type b polysaccharide conjugated to tetanus protein, diphtheria, tetanus, pertussis, and inactivated poliovirus vaccines (types 1, 2, and 3)	$ 1.5 billion	Sanofi and Sanofi Pasteur MSD
Gardasil®	Human papillomavirus quadrivalent (types 6, 11, 16, and 18) vaccine, recombinant	$ 1.4 billion	Merck & Co. and Sanofi Pasteur MSD
Infanrix/Pediarix	Diphtheria and tetanus toxoids and acellular pertussis adsorbed, hepatitis B (recombinant) and inactivated poliovirus vaccine combined	$ 1.1 billion	GlaxoSmithKline
Fluzone®, Fluzone High-Dose and Fluzone Intradermal /Vaxigrip®/ Mutagrip®	Influenza virus vaccine	$ 1.1 billion	Sanofi and Sanofi Pasteur MSD

Source: "Top 15 Vaccines of 2012," *Genetic Engineering & Biotechnology News*, July 8, 2013, http://www.genengnews.com/insight-and-intelligenceand153/top-15-vaccines-of-2012/77899844/, accessed August 2013.

Exhibit 7 Key Facts on GAVI

a) Main Goals



Source: WHO, "History of Vaccine Development," WHO Website, http://www.vaccine-safety-training.org/history-of-vaccine-development.html, accessed November 2013.

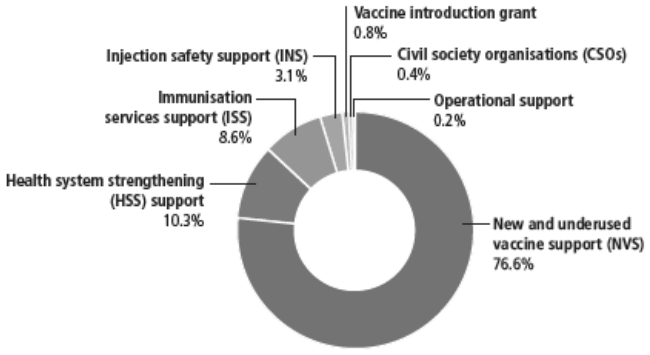
Note: EPI = WHO's Expanded Program on Immunization.

b) GAVI Vaccine Support (2011)

GAVI Vaccine Support	
Currently supported vaccines	*Routine:* Pentavalent, pneumococcal, rotavirus, human papillomavirus (HPV), yellow fever, measles second dose
	Campaign: Yellow fever, meningococcal A conjugate, measles, rubella
	Stockpile: Meningitis and yellow fever vaccines for outbreak response
Prioritized for future support	Japanese encephalitis and typhoid conjugate vaccines
Monitoring development	Malaria, dengue

Source: Jon Pearman, "Basic Facts about the GAVI Alliance," PowerPoint presentation, May 19, 2013, http://www.whcaonline.org/uploads/WHEN%202013/Pearman%20-WHA%20%20GENEVA%202013.pptx, accessed November 2013.

c) Disbursements to Countries by Type of Support (2000–2011)



Source: GAVI, Progress Report 2011 (Geneva: GAVI, 2011), p. 9, http://www.gavialliance.org/results/gavi-progress-reports/, accessed November 2013.

Exhibit 7 (continued)

d) GAVI Disbursements by Year Paid (US$ thousands, 2000–2011)

	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Country Programs												
Civil Society Organizations									4,827	6,129	2,714	1,580
Health System Strengthening								92,011	138,389	33,877	50,370	43,578
Injection Safety Support			13,949	27,346	20,673	27,770	3,439	9,439	5,067	115		
Immunization Services Support	1,987	5,872	9,080	22,150	34,668	50,711	43,746	49,579	43,157	4,761	25,326	7,509
New and Underused Vaccine Support		108,015	67,657	107,929	79,745	126,722	146,763	235,553	393,470	288,110	504,465	614,458
Operational Support												7,571
Vaccine Introduction Grant		400	3,560	960	1,060	920	100	1,100	9,799	2,331	1,532	5,753
Investment Cases	0	0	0	6,455	6,342	15,811	19,284	434,471	17,294	39,049	66,377	9,529
Total	**1,987**	**114,287**	**94,246**	**164,840**	**142,488**	**221,934**	**213,332**	**822,153**	**612,003**	**374,372**	**650,784**	**689,978**

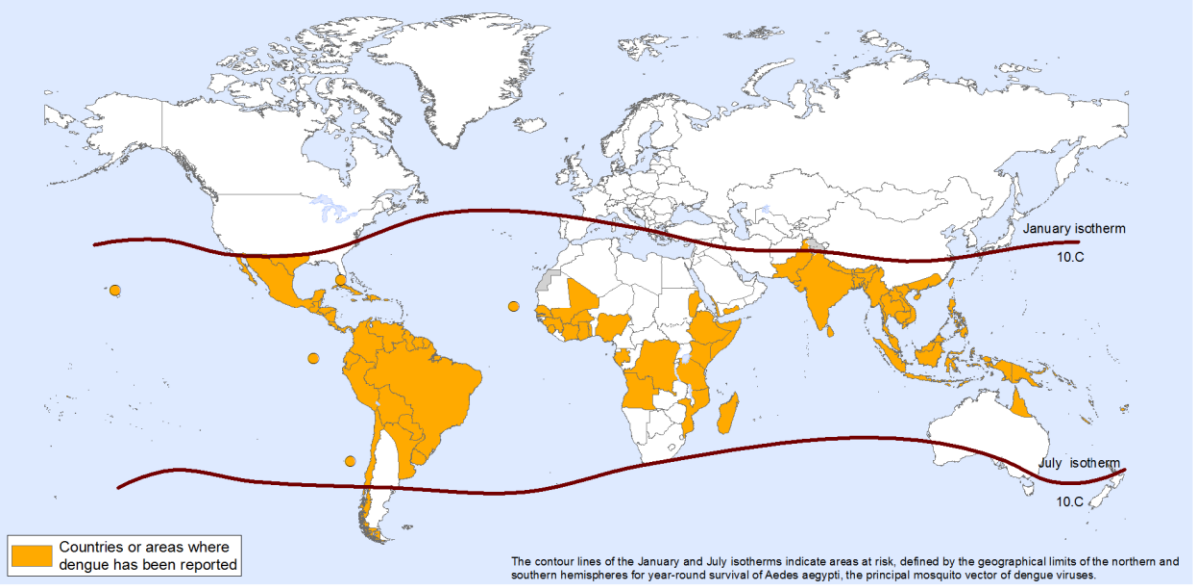
Source: GAVI, "Disbursements by Country," GAVI Website, http://www.gavialliance.org/results/disbursements/, accessed November 2013.

Note: These amounts were net amounts, including return of unused funds from UNICEF as a result of obtaining lower supply or freight prices than originally estimated.

Investment case disbursements were onetime tactical investments in disease prevention and control that were made through GAVI partners such as UNICEF and WHO. Each investment targeted a disease that constrained progress toward the United Nations Millennium Development Goals for improved child and maternal health.

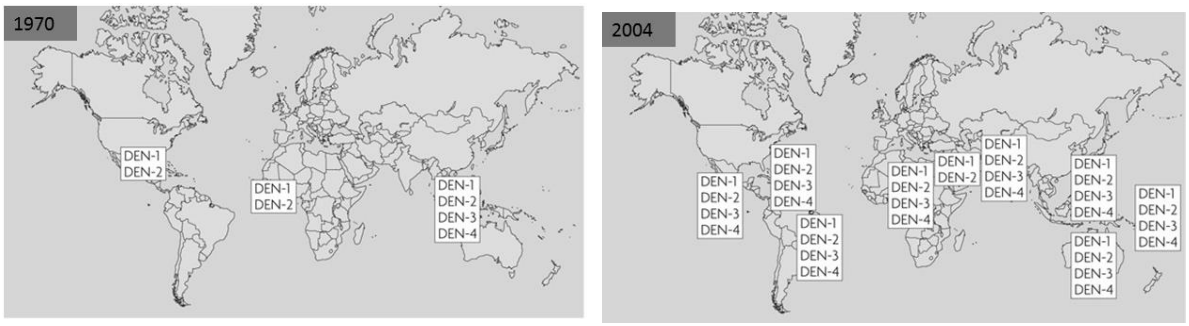
Exhibit 8 Dengue Maps

a) Areas at Risk for Dengue (2013)



Source: Reproduced with permission from the World Health Organization, 2014, http://gamapserver.who.int/mapLibrary/Files/Maps/Global_DengueTransmission_ITHRiskMap.png, accessed July 2014.

b) Change in Distribution of Dengue Serotypes



Source: M. G. Guzman et al., "Dengue: A continuing global threat," *Nature Reviews Microbiology* 8 (2010): S7–S16, http://www.nature.com/scitable/content/the-change-in-distribution-of-dengue-serotypes-22401317, accessed November 2013.

Exhibit 9a Dengue Vaccine Development Timeline

Date	Facts
1994	Partnership between Sanofi Pasteur and the Vaccine Development Centre, University of Mahidol (Bangkok – Thailand).
2001	Proof of concept of a tetravalent live attenuated dengue vaccine in two doses and a booster. Start of the development of a second-generation vaccine obtained by recombinant technology.
2004	Classical live vaccine approach abandoned due to reactogenicity and under-attenuation of serotype 3. Sanofi Pasteur decides to adopt a new approach, with a second-generation live attenuated vaccine.
2006	Partnership with PDVI (Pediatric Dengue Vaccine Initiative), a consortium working to accelerate the introduction of a dengue vaccine for children in endemic countries (supported by the Bill & Melinda Gates Foundation).
2007	Positive results in Phase II clinical studies; proof of concept.
2009	Sanofi Pasteur dengue vaccine enters pediatric clinical efficacy study in Thailand.
June 2010	The U.S. FDA grants fast track status to Sanofi Pasteur candidate dengue vaccine.
Oct. 2010	Sanofi Pasteur dengue vaccine enters Phase III clinical study.
Feb. 2011	Partnership with the International Vaccine Institute to support the DVI (Dengue Vaccine Initiative), a non-profit advocacy group focused on raising awareness of dengue fever and supporting the introduction of dengue vaccination, funding by the Bill & Melinda Gates Foundation.

Source: Company documents.

Exhibit 9b Main Dengue Vaccine Candidates (as of February 2012)

Approach	Developer	Status
Live attenuated virus *YF17D/DEN chimeric*	Sanofi Pasteur	Phase III tetravalent
Live attenuated virus *Serial cell passage*	GSK/WRAIR	Phase II tetravalent
Live attenuated virus *DEN/DEN chimeric*	Inviragen	Phase II tetravalent
Live attenuated virus *Targeted mutations DEN/DEN chimeric*	NIH (Licensees: Biological E, Panacea, Butantan, Vabiotech)	Phase I tetravalent
Recombinant subunit *80% E*	Merck	Phase I tetravalent
DNA *prM/E*	NMRC/WRAIR	Phase I tetravalent
Purified inactivated virus	GSK/Oswaldo Cruz Foundation	Phase I monovalent

Source: Monika Simmons, Nimfa Teneza-Mora, and Robert Putnak, "Advances in the development of vaccines for dengue fever," *Vaccine: Development and Therapy*, May 2, 2012, accessed August 2013.

Exhibit 10 Vaccine Demand in Selected Dengue-Endemic Countries

a) Selected Key Facts (2010)

Selected Endemic Countries	Reported[a] Number of Dengue Cases	Reported[a] Number of Dengue-Related Deaths	Estimated Costs of the Disease (US$ million — PPP adjusted)[c]	Population (thousands)	Tourist Arrivals (thousands)	GDP per Capita (current US$)	Health Expenditure per Capita (current US$)
GAVI- eligible							
Vietnam	128,831	55	364	89,038	5,050	1,224	$83
Lao PDR	22,929	46	48	6,434	1,670	1,123	$30
Myanmar	16,529	2	13	60,280	311	742	$17
Cambodia	12,500	38	24	15,042	2,508	783	$48
GAVI-noneligible							
Brazil	1,004,392	673	2,230	191,480	5,161	10,978	$990
Colombia	157,152	217	900	22,939	2,681	6,180	$407
Indonesia[b]	155,777	1,358	315	237,641	7,033	2,947	$84
Philippines	135,355	591	446	93,639	3,520	2,136	$89
Venezuela	123,967	0	1,181	28,384	526	13,559	$720
Thailand	116,947	139	470	69,122	15,936	4,803	$179
Honduras[b]	66,814	83	268	6,575	863	2,020	$176
Mexico	57,971	20	783	110,619	23,290	8,780	$603
Malaysia	46,171	33	645	27,935	24,577	8,729	$368
India	28,292	96	76	1,150,000	5,776	1,419	$51
Puerto Rico	21,298	33	735	3,952	3,186	26,106	N/A
Paraguay	13,553	15	63	6,451	465	3,101	$272
Singapore	5,364	4	304	4,855	9,161	42,784	$2,005
United States	65	0	N/A	308,745	59,796	46,616	$8,233

Source: Except as noted to the contrary: compiled data from the World Health Organization, the Pan American Health Organization, and the United Nations, accessed June 13, 2013. Estimated costs of the disease: UPMC Center for Health Security, accessed June 14, 2013. Arrivals of Non-Resident Tourists: World Tourism Organization, accessed June 13, 2013. GDP per capita and Health Expenditure per capita: World Bank, accessed September 19, 2013.

[a] The table is based on the number of reported cases. Dengue is underreported for a number of reasons, including the following: Many individuals with classic dengue fever do not present for care. Dengue fever is a flulike illness and can be difficult to diagnose. Not all diagnosed cases are reported to public health or health ministry officials. Not all countries collect and report dengue incidence publicly. Dengue reporting systems vary by country and any change in the surveillance system over time is not reflected in the above figures. Some observers believe that there are other factors accounting for the difference between WHO estimates and the number of cases reported above. The huge disparities should make one wonder about the value of these figures.

[b] GAVI (Global Alliance for Vaccines and Immunization)–eligible countries: countries with GNI per capita below US$1,500. Indonesia and Honduras are currently graduating from GAVI support.

[c] Total costs for individual countries were calculated by adding the direct and indirect costs associated with case incidence. Costs are reported in purchasing power parity (PPP)–adjusted 2010 US$. Cost estimates were derived from established economic theory, were informed by previous infectious disease cost models, and include, among others, dengue hospital (inpatient) costs, dengue clinic costs, dengue productivity costs, and dengue costs due to death.

Exhibit 10 (continued)

b) Estimated Dengue Vaccine Doses (millions) Required for Routine Early Childhood and Catch-up Vaccination, Public Sector, Five-year Period after Licensure[a] (based on 2008 data)

	Routine Early Childhood (12–23 months)[a]	Catch-up, 2–4 yr. Cohort	Catch-up, 2–14 yr. Cohort
All dengue-endemic countries			
GAVI-eligible[b]			
Low income	109	74	331
Low-middle income	290	263	1,128
Upper-middle income	2	1	6
Subtotal	*401*	*338*	*1,465*
GAVI-noneligible[b]			
Low-middle income	97	73	290
Upper-middle income	142	84	377
High income	6	4	18
Subtotal	*245*	*161*	*685*
Total doses	646	499	2,150
Early adopters of dengue vaccine[c]			
Low-middle income	47-57	31-37	121-156
Upper-middle income	107-128	61-73	254-329
High income	1.6-1.7	1.1-1.4	4.3-5.6
Total doses	156-187[d]	93-111[d]	380-490[d]

Source: A. Amaransinghe, O. Wichmann, H. S. Margolis, and R. T. Mahoney, "Forecasting dengue vaccine demand in disease endemic and non-endemic countries," *Human Vaccines* 6, no. 9 (September 2010).

[a] Assumes rapid adoption and integration into national immunization program and Expanded Program on Immunization. The upper-limit projections should be considered optimistic since no vaccine in recent history has experienced such a widespread adoption rate for reasons that include delays in country licensure, lack of national immunization program infrastructure to incorporate a new vaccine, and lack of vaccine financing.

[b] GAVI (Global Alliance for Vaccines and Immunization)–eligible countries: countries with GNI per capita below or equal to US$1,500 (as of 2008). Income category according to World Bank, 2008. GAVI-eligible countries: **Low income** (Afghanistan, Bangladesh, Cambodia, Haiti, Lao PDR, Myanmar, Nepal, Vietnam); **Low-middle income** (Bolivia, Guyana, Honduras, India, Indonesia, Kiribati, Nicaragua, Pakistan, Papua New Guinea, Solomon Islands, Sri Lanka, Timor Leste); **Upper-middle income** (Cuba). GAVI-noneligible countries: **Low-middle income** (Belize). Please note that GAVI-eligibility criteria have changed; several eligible countries in 2008 are no longer eligible in 2012.

[c] Early-adopter countries: Income category according to World Bank, 2008. **Low-middle income countries**: Federated States of Micronesia, Nicaragua, Philippines, Sri Lanka, Thailand, Tongo; **Upper-middle income countries**: Argentina, Brazil, Colombia, Costa Rica, Cuba, Fiji, Malaysia, Mexico, Panama; **High-income countries**: New Caledonia, North Queensland, Polynesia, Singapore, U.S. EPI–covered areas.

[d] Ranges are for 10% and 25% wastage assumptions, respectively.

Exhibit 10 (continued)

c) Estimated Dengue Vaccine Doses (millions) by Market Sector and Vaccination Schedule, Five-Year Period after Vaccine Licensure (based on 2008 data)

	Totals
Public market sector	
Endemic countries [A]	2,695[a]
Early-adopter countries [B]	636[a]
Private market sector [C]	664
Travelers market [D]	89
Scenarios	
All dengue-endemic countries and Travelers [A+C+D]	3,448
Early-adopter countries and Travelers [B+C+D]	1,389

Source: A. Amaransinghe, O. Wichmann H. S. Margolis, and R. T. Mahoney, "Forecasting dengue vaccine demand in disease endemic and non-endemic countries," *Human Vaccines* 6, no. 9 (September 2010).

[a] Includes routine vaccination of the 12- to 23-month cohort and catch-up vaccination of 2- to 14-year cohort. Excludes 2- to 14-years age group estimates of private sector, and numbers deviate therefore from those presented in the previous exhibit. Public-sector vaccine wastage: 25%.

Exhibit 11 Examples of Tiered Pricing (2012)

Vaccine	U.S. Price per Dose (US$, 2012)		Weighted Average per Dose (US$, 2012)	
	Private Sector	**CDC[a] (public)**	**UNICEF GAVI[b]**	**PAHO[a] Revolving Fund[b]**
Diphtheria and tetanus toxoids *(Pediatric)*	Sanofi: $21.74[c]	Sanofi: $17.57[c]	$0.10	$0.08
Diphtheria, Tetanus, Pertussis – Hepatitis B - Haemophilus influenzae type B *(liquid)*	N/A	N/A	$2.50 - $3.20	$2.98
Hepatitis A *(Adult, two-dose schedule)*	GSK: $63.72 Merck: $59.98	GSK: $25.00 Merck: $22.09	N/A	$11.00
Hepatitis A *(Pediatric, two-dose schedule)*	Merck: $30.36 GSK: $28.74	Merck: $15.25 GSK: $15.63	N/A	$7.10
Hepatitis B *(Adult)*	GSK: $52.50 Merck: $59.09	GSK: $24.63 Merck: $24.23	$0.40	$0.36
Hepatitis B *(Pediatric)*	GSK: $21.37 Merck: $23.20	GSK: $10.93 Merck: $11.00	N/A	$0.24
HPV *(Quadrivalent Human Papillomavirus Types 6, 11, 16 and 18 Recombinant)*	Merck: $135.45	Merck: $107.15	$4.50	$14.25
HPV *(Bivalent Human Papillomavirus Types 16 and 18)*	GSK: $128.75	GSK: $100.85	$4.60	$13.48
Measles, Mumps and Rubella (T*wo-dose schedule)*	Merck: $56.13 *(Pediatric)* Merck: $56.13 *(Adult)*	Merck $19.75 *(Pediatric)* Merck: $37.67 *(Adult)*	$1.95 $3.10	$1.85 $ 3.50
Pneumococcal Pediatric *(13-valent, three- or four-dose schedule)*	Pfizer: $128.16	Pfizer: $107.12	$7.00	$16.34 *(Conjugate)*
Rotavirus *(liquid, two-dose schedule)*	GSK: $106.57	GSK: $92.15	N/A	$6.88
Rotavirus *(liquid, three-dose schedule)*	Merck: $75.203	Merck: $63.961	N/A	$5.25

Source: Compiled from CDC, http://www.cdc.gov/vaccines/programs/vfc/awardees/vaccine-management/price-list/#f5; Unicef, http://www.unicef.org/supply/index_57476.html; and PAHO https://www.google.fr/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&cad=rja&ved=0CD4QFjAB&url=http%3A%2F%2Fwww.paho.org%2Fhq%2Findex.php%3Foption%3Dcom_docman%26task%3Ddoc_download%26gid%3D17031%26Itemid%3D&ei=tdlTUtfdCMem0QXujIHQBg&usg=AFQjCNHNyKXaIxGf3H2P1x2PflXAuyAyVA), accessed October 2013.

[a] CDC = Centers for Disease Control. PAHO = Pan American Health Organization.

[b] UNICEF and PAHO do not specify the manufacturers for the vaccines they are purchasing. All vaccines are recommended for a three-dose schedule, unless stated otherwise.

[c] Sanofi indicates that this is a one-dose vial.

Endnotes

[1] World Health Organization, "Dengue and Severe Dengue," World Health Organization Website, http://www.who.int/mediacentre/factsheets/fs117/en/index.html, accessed October 2013.

[2] Simeon Bennett, "Sanofi Dengue Bid Seen as $2.6 Billion Hit or Major Flop," Bloomberg, August 5, 2013, http://www.bloomberg.com/news/2013-08-04/sanofi-dengue-bid-seen-as-2-6-billion-hit-or-major-flop.html, accessed August 2013.

[3] Ibid.

[4] Armelle Bohineust, "Jean-François Dehecq quitte Sanofi-Aventis," Le Figaro.fr, May 17, 2010, http://www.lefigaro.fr/societes/2010/05/16/04015-20100516ARTFIG00201-jean-francois-dehecq-quitte-sanofi-aventis.php, accessed June 2013.

[5] Reference for Business, "History of Sanofi Group," Reference for Business Website, http://www.referenceforbusiness.com/history2/37/SANOFI-GROUP.html, accessed August 2013.

[6] Ibid.

[7] Valérie Lion, "Sanofi-Aventis, les remèdes d'un géant," *L'Express,* May 17, 2010, http://www.lexpress.fr/actualite/economie/sanofi-aventis-les-remedes-d-un-geant_892686.html, accessed June 2013.

[8] Standard & Poor's Compustat data, via Capital IQ, accessed August 2013.

[9] "Sanofi-Aventis se rebaptise Sanofi," Le Figaro.fr, May 4, 2011, http://www.lefigaro.fr/flash-eco/2011/05/04/97002-20110504FILWWW00450-sanofi-aventis-se-rebaptise-sanofi.php, accessed June 2013.

[10] Standard & Poor's Compustat data, via Capital IQ, accessed August 2013.

[11] Alison Sahoo, "Vaccines 2012," Kalorama Information Market Intelligence Report, September 2012, http://academic.marketresearch.com, accessed June 2013.

[12] Till Bärnighausen, David E. Bloom, Elizabeth T. Cafiero, and Jennifer C. O'Brien, "Valuing the broader benefits of dengue vaccination, with a preliminary application to Brazil," Semin Immunol, 2013, http://dx.doi.org/10.1016/j.smim.2013.04.010, accessed September 2013.

[13] Jon Evans, "Vaccine Production 2012," Kalorama Information Market Intelligence Report, February 2012, http://academic.marketresearch.com, accessed June 2013.

[14] Ibid.

[15] Paul Wilson, *Giving developing countries the best shot: An overview of vaccine access and R&D* (Geneva: Médecins Sans Frontières, 2010), http://www.msf.org.uk/sites/uk/files/Vaccine_Report_201005111518.pdf, accessed November 2013.

[16] Evans, "Vaccine Production 2012."

[17] Pierre Morgon, "Vaccines: Poised to deliver significant growth in emerging markets," Sanofi PowerPoint presentation, May 17, 2011, http://www.dvfa.de/fileadmin/downloads/Verband/Kommissionen/Life_Science/2011/sanofi_pasteur_morgon.pdf, accessed December 2013.

[18] Phacilitate, "Partnering for Vaccine, Emerging Markets," Phacilitate Website, June 10, 2013, http://www.vaccineemergingmarkets.com/programme-day-1/, accessed December 2013.

[19] "Vaccines 2012," Kalorama Information Market Intelligence Report, September 2012.

[20] GAVI Alliance, "Countries eligible for support," GAVI Alliance Website, http://www.gavialliance.org/support/apply/countries-eligible-for-support, accessed June 2013.

[21] GAVI Alliance, 2011 Annual Financial Report (Geneva: GAVI Alliance, 2012), p. 8.

[22] GAVI Alliance, "Procurement policy," GAVI Alliance Website, http://www.gavialliance.org/about/governance/corporate-policies/procurement/, accessed December 2013.

[23] Daniel Rodriguez, "The PAHO Revolving Fund and the Access to Seasonal Influenza Vaccine in the Americas," World Health Organization Website, 2013, http://www.who.int/influenza_vaccines_plan/resources/session_6_rodriguez.pdf, accessed December 2013.

[24] Pan American Health Organization (PAHO), "The Revolving Fund as a Technical Cooperation Mechanism for Immunization Programs in the Americas," PAHO Website, 2013, accessed December 2013.

[25] World Health Organization, "Dengue and Severe Dengue," World Health Organization Website, http://www.who.int/mediacentre/factsheets/fs117/en/index.html, accessed October 2013.

[26] Ibid.

[27] Scott Hensley, "Dengue Fever pops up in Florida," NPR, August 26, 2013, http://www.npr.org/blogs/health/2013/08/26/215789614/dengue-fever-pops-up-in-florida, accessed August 2013.

[28] World Health Organization, "Dengue and Severe Dengue."

[29] World Health Organization, "Dengue control: the mosquito," World Health Organization Website, http://www.who.int/denguecontrol/mosquito/en/index.html, accessed August 2013.

[30] World Health Organization, "Dengue control: the human," World Health Organization Website, http://www.who.int/denguecontrol/human/en/index.html, accessed August 2013.

[31] World Health Organization, "Dengue and Severe Dengue."

[32] World Health Organization, "Dengue control: control strategies," World Health Organization Website, http://www.who.int/denguecontrol/control_strategies/en/, accessed August 2013.

[33] World Health Organization, "Dengue control: environmental strategies," World Health Organization Website, http://www.who.int/denguecontrol/control_strategies/environmental_management/en/index.html, accessed August 2013.

[34] World Health Organization, "Dengue control: chemical control," World Health Organization Website, http://www.who.int/denguecontrol/control_strategies/chemical_control/en/index.html, accessed August 2013.

[35] World Health Organization, "Dengue control: biological control," World Health Organization Website, http://www.who.int/denguecontrol/control_strategies/biological_control/en/index.html, accessed August 2013.

[36] Till Bärnighausen et al., "Valuing the broader benefits of dengue vaccination, with a preliminary application to Brazil."

[37] Arturo Cuevas, "Healthier Days Loom as 3 Big Pharmas Move on Dengue Shots," post on blog "The Motley Fool Blog Network," August 12, 2013, http://beta.fool.com/darttanyan001/2013/08/12/whod-win-in-pharma-war-on-a-femme-fatale/42691/, accessed November 2013.

[38] Robert Herriman, "Inviragen CEO, Dr. Dan Stinchcomb Gives An Update On The DENVax Dengue Fever Vaccine," January 14, 2013, *Global Dispatch*, http://www.theglobaldispatch.com/inviragen-ceo-dr-dan-stinchcomb-gives-an-update-on-the-denvax-dengue-fever-vaccine-24841/, accessed August 2013.

[39] Julia Schmitz, John Roehrig, Alan Barrett, and Joachim Hombach, "Next generation dengue vaccines: A review of candidates in preclinical development," *Vaccine* 29 (2011): 7276–7284, accessed August 2013.

[40] Simeon Bennett, "Sanofi Dengue Bid Seen as $2.6 Billion Hit or Major Flop."

[41] Ibid.

[42] Ananda Amarasinghe, Ole Wichmann, Harold S. Margolis, and Richard T. Mahoney, "Forecasting dengue vaccine demand in disease endemic and non-endemic countries," Pediatric Dengue Vaccine Initiative (PDVI) and International Vaccine Institute, Seoul, Korea, *Human Vaccines* 6, no. 9 (September 2010): 745–753, accessed August 2013.

[43] Dengue Vaccine Initiative (DVI), "Planning for the Introduction of Dengue Vaccines," DVI Website, April 19–20, 2011, p. 1, http://www.denguevaccines.org/sites/default/files/APDPBReport_Hanoi_April2011.pdf, accessed August 2013.

[44] "Developing Strategies for Meeting the Challenge of Equitable Vaccine Introduction in the Americas: With a Focus on Dengue Vaccine Financing," Proceedings of the 2013 PAHO workshop, Washington, DC, July 22–23, 2013, p. 83.

[45] Geoffrey Dow and Eric Mora, "The maximum potential market for dengue drugs," *Antiviral Research* 96 (2012): 203–212, accessed August 2013.

[46] "Vaccine for dengue is within sight, but demand will exceed supply," *The Guardian*, April 19, 2011, http://www.theguardian.com/global-development/2011/apr/19/dengue-vaccine-within-sight-demand-supply, accessed August 2013.

[47] Ben Hirschler, "Dengue vaccine in sight, after 70 years," Reuters, June 6, 2012, http://in.reuters.com/article/2012/06/05/dengue-vaccine-idINDEE8540I820120605, accessed August 2013.

[48] Arunee Sabchareon et al., "Protective efficacy of the recombinant, live-attenuated, CYD tetravalent dengue vaccine in Thai schoolchildren: a randomised, controlled phase 2b trial," *The Lancet*, September 11, 2012, http://press.thelancet.com/denguevaccine.pdf, accessed August 2013.

[49] Ben Hirschler, "Sanofi dengue vaccine less effective than hoped," Reuters, September 10, 2012, http://www.reuters.com/article/2012/09/10/us-sanofi-dengue-idUSBRE8891CJ20120910, accessed August 2013.

[50] Geoffrey Dow and Mora, "The maximum potential market for dengue drugs."

[51] "Perspectives from Industry: Tiered Pricing and Vaccine Access: An Interview with Mark Feinberg, Suresh Jadhav, and Jean Stéphenne," National Bureau of Asian Research, February 2012, http://www.pacifichealthsummit.org/downloads/Impact%20&%20Innovations/Vaccine_Tiered_Pricing.pdf, accessed August 2013.

[52] Ibid.

[53] Ibid.

[54] Don L. Douglas, Denise A. DeRoeck, Richard T. Mahoney, and Ole Wichmann, "Will Dengue Vaccines Be Used in the Public Sector and if so, How? Findings from an 8-country Survey of Policymakers and Opinion Leaders," PLoS Neglected Tropical Diseases Working Paper 7(3): e2127. doi:10.1371/journal.pntd.0002127, 2013, accessed August 2013.