Antiviral Research 96 (2012) 203–212

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

The maximum potential market for dengue drugs V 1.0

Geoffrey Dow [a,*], Eric Mora [b]

[a] 60° Pharmaceuticals LLC, 1025 Connecticut Ave. NW, Washington, DC 20036, United States
[b] PreSight Healthcare Solutions, 6118 11th Rd. N, Arlington, VA 22205, United States

ARTICLE INFO

Article history:
Received 25 May 2012
Revised 24 August 2012
Accepted 25 August 2012
Available online 8 September 2012

Keywords:
Dengue
Market
Economic burden
Tiered pricing
Dengue drug
Dengue vaccine

ABSTRACT

Drugs offer a complementary approach to vaccines for preventing the progression of symptoms and onset of the severe manifestations of dengue. Despite the rapid maturation of the research and development infrastructure for dengue drugs and the increasing frequency of dengue inhibitors reported in the scientific literature, the potential size of the market for dengue drugs has not been articulated. In the present work, extrapolating from publicly available information, we explored the economic burden attributable to dengue, the impact of dengue vaccines on clinical case loads, a possible alternative to tiered pricing for products for neglected diseases, and defined the maximum potential market for a dengue drug. Our projections suggest that in 2006, the annual global burden of dengue was US $1.7 billion. Our proposed alternative to existing tiered pricing structures is that during a temporary period of market exclusivity, individual countries would pay 50% of the per-case equivalent of economic costs saved through the use of a dengue drug. This would yield prices per case of US $13–$239 depending on drug effectiveness and cost of medical and indirect costs and lost productivity in different countries. Assuming that such a pricing scheme was embraced, the maximum potential market for a dengue drug or drugs that on average reduced 40% of economic costs might be as high as US $338 million annually. Our simulations suggest that dengue vaccines will begin to reduce the clinical case load of dengue in 2022, but that the number of cases will not decrease below 2006 levels and the proportion vaccinated will remain well below that required for the onset of herd immunity during the period of market exclusivity after the licensure of the first wave of dengue drugs.

1. Introduction

Approximately 2.5–3.5 billion of the world's population is at risk of contracting dengue (TDR, 2009; WHO, 2012a). Estimates of the number of new infections range from 50 to 230 million annually (Sanofi, 2009; WHO, 2012a) of which approximately a quarter are sufficiently debilitating to require medical attention (reviewed by Shepard et al., 2004). Approximately 3–6% of clinical cases progress from an acute but uncomplicated febrile form of the disease to dengue hemorrhagic fever or dengue shock syndrome (Shepard et al., 2004; WHO, 2012a). This manifestation of the disease may be fatal. The death toll based on official estimates is approximately 12,500 (WHO, 2012a), but is likely substantially higher as the majority of cases are not officially reported (see summary in Suaya et al., 2009).

A number of dengue vaccines are in development (Coller et al., 2011; Danko et al., 2011; Durbin et al., 2011; Guy et al., 2011; Osorio et al., 2011). This has inspired a body of work related to the economic costs of the disease (see review by Beatty et al., 2011). Suaya et al. (2009) described the medical and non-medical costs of severe and uncomplicated dengue in ambulatory and hospital settings in eight countries in South America and South East Asia, and estimated the burden of dengue in these countries to be $238 million annually based on official case reports. This study also projected the potential economic burden within a limited geographic range using various multipliers for unreported cases. This study did not attempt to describe the global burden of dengue, or the economic benefit that might be created by a dengue drug or vaccine. This was one of the objectives of the present study.

It is more likely than not that a dengue vaccine (Guy et al., 2011) will be approved and available for distribution by 2015. Four other vaccines, which are licensed to a total of seven companies or institutions, are in early clinical development. These other vaccines may come into production between 2017 and 2021 if successfully developed and approved by regulators. Based on results from Phase IIB studies, dengue vaccines are expected to be effective (Sanofi, 2012). Annual plant capacity of the first vaccine will be limited to 100 million doses (Sanofi, 2009) which is sufficient to vaccinate 33 million assuming a three dose regimen and no wastage. Given that the at-risk population is 2.5–3.5 billion one would suspect that this level of vaccination may be unlikely to result in a substantial reduction in dengue cases in the short term. Access

* Corresponding author. Tel.: +1 240 351 1167; fax: +1 202 688 2832.
E-mail address: geoffdow@60degreespharma.com (G. Dow).

0166-3542/$ - see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.antiviral.2012.08.011

may be further limited if manufacturers are forced to price the vaccine too high in endemic countries or market the vaccine to developed country travelers in order to recover research and development costs. The prospect of antibody-dependent enhancement, if it eventuated, would further limit the impact of vaccines.

Drugs are a complementary intervention that may be useful for patients who contract dengue because they did not receive an approved dengue vaccine or for whom prior vaccination was ineffective. A dengue drug would be useful to a patient if, when administered after a clinical diagnosis of dengue, it resolved symptoms and/or prevented progression to dengue hemorrhagic fever or dengue shock syndrome. Such a drug would also reduce or eliminate the associated medical and indirect economic costs for individual patients and government health systems. However, the unmet medical need for a dengue drug might be limited if sufficient dengue vaccines are available at reasonable cost and the annual case rate is reduced nearly to zero. Therefore another objective of this study was to simulate the effect of vaccine introduction on annual case loads during the time frame of the potential introduction of a dengue drug.

One of the most vexing issues in the marketing of drugs in emerging markets is the issue of pricing. Tiered pricing, where a drug is priced in two or three different bands for countries based on GDP, has evolved as the global standard in response to sustained community pressure for greater patient access to drugs (Moon et al., 2011). However, this convention has recently been critiqued as arbitrary and fails to account for income inequality within countries that are nominally middle income (discussed by Moon et al., 2011). The alternative is to segment the market into public and private sectors, but this approach may be inefficient and difficult to implement (Moon et al., 2011). A third approach is for a company to maintain the price in emerging markets at prices approaching the variable costs of manufacturing. This maintains prices at lower levels, but has been criticized as being anti-competitive (Moon et al., 2011). Therefore, the final objective of this study was to explore an alternative pricing scheme based on an objective, equitable distribution of the economic savings of drug intervention with the intent of defining the maximum potential market for dengue drugs.

2. Methods

2.1. Global economic burden of dengue

Diseases impose an economic burden on society that includes direct medical costs to the health system or individuals, non-medical 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). The per-case economic burden of dengue, using these cost inputs, has been reported by Suaya et al. (2009) and others for eight countries in Asia and the Americas, representing 64% of the global burden of this disease. We used these input data to determine the economic burden of dengue in these countries based on the number of reported cases (Table 1).

We estimated the total and by segment cost per case and economic burden in the rest of the world (ROW, Table 1, right column) by adjusting for official caseload and on average threefold lower GDP per capita in other dengue markets (economic burden in countries studied by Suaya et al.∗.36/.64∗.33). For each of the four market segments (ambulatory versus hospitalization and public versus private) we then calculated an average cost per case (total burden/total number of cases, see Table 2). This was further adjusted to take into account the threefold lower GDP in countries not covered by Suaya et al. (2009), see Table 2. We also calculated a weighted average of the proportion of cases in each market segment based on caseloads reported by Suaya et al. (2009), see Table 2.

However, official reported cases of dengue under-estimate the number of clinical cases of the disease (discussed by Suaya et al., 2009), so the global economic burden of dengue reported based on reported cases is conservative. Therefore, we adjusted the global caseload and economic burden upwards by a factor of 6, to account for unreported cases (Armien et al., 2008). The same assumptions regarding dengue case loads and adjustments for unreported cases were also made for the vaccine impact model (next Section). Our estimates for global clinical case load, economic burden, and weighted average cost per case are presented in Table 3 (top three rows).

2.2. Vaccination rates and clinical case load following the introduction of dengue vaccines

A dengue drug will have clinical utility if the availability and market penetration of dengue vaccines is insufficient to eliminate transmission of dengue. We constructed a Monte Carlo Simulation model (10,000 simulations) using Oracle Crystal Ball® to project future dengue case loads based on current trends and publicly available information about dengue vaccines. The key assumptions of the model including distributions, most likely, minimum and maximum values are summarized in Table 4. Generally we have assumed a normal distribution, with a standard deviation of 10% around the most likely value, except where there was specific information from the literature that suggested an alternative distribution might be appropriate. More details regarding some of the assumptions are outlined below.

Sanofi's tetravalent dengue vaccine is in Phase III trials. We selected a probability of successful completion of the Phase III program and licensure at 75% based on our perception of industry norms for a typical biotech product. A launch of date of 2015 is feasible if there are no delays in Sanofi's development program. Inviragen, GSK, and Merck all have dengue vaccines in development, and NIH, has licensed its technology to four institutions or companies regionally. These other efforts appear to be in late Phase I or early Phase II, and so could in theory be licensed in a 2017–2021 time window if development plans remain on track. Therefore, we selected the most likely licensure date as 2019, with minimum and maximum ranges of 2017 and 2021. We have assumed that the probability of achieving licensure for each of these vaccines is approximately 21% (35% probability of success in Phase II $\times$ 60% probability of success in Phase III) based on industry norms for a typical biotech product in early clinical development (Zemmel and Shiekh, 2010). The probability of discrete numbers (0–7) of additional vaccines being approved was then calculated.

We have assumed that the volume of dengue vaccine doses sold will be limited by capacity, and that the price of dengue vaccines that is negotiated will be set in a manner that will allow the available capacity to be sold. Sanofi has publicly stated that their plant capacity will be 100 million doses annually, which is vastly less than the number of doses that would be required to vaccinate the entire population given that a three dose regimen will be required. Given the scale of the investment involved, 350 million euros for the plant alone (Sanofi, 2009), Sanofi as a publicly traded company would be legally required to disclose a decision to substantially increase capacity. Unlike small molecules, for which capacity given sufficient resources is in theory limitless, the production and regulation of a biologic is inherently connected to a specific physical plant. A decision to increase capacity beyond incremental increases would require at least four years of lead time and a similar level of investment as existing capacity. Therefore, we have assumed that any decision to increase capacity by Sanofi or other potential manufacturers will only occur after the successful licensure of at least one vaccine and when vaccine pricing strategies become clearer.

Table 1
Country level break-down of per-case dengue costs, case disposition and medical setting. All costs are in 2006 $US. Source data are from Suaya et al. (2009).

Parameter	Market								Average	ROW estimate
	Americas					Asia				
	Brazil	El Salvador	Guatemala	Panama	Venezuela	Cambodia	Malaysia	Thailand		
Total average cost of an ambulatory case ($)	291	88	88	332	168	-	317	-	199	66
Total average cost of a hospitalization case ($)	676	457	418	1065	627	115	947	573	600	198
Average direct medical costs of an ambulatory case ($)	37	22	19	63	60	–	193	–	71	24
Average direct medical costs of a hospitalization case ($)	290	323	327	559	438	28	752	468	414	136
Proportion of ambulatory cases in private sector (%)	49	5	30	22	24	0	19	0	14	14
Proportion of hospitalization cases in private sector (%)	47	0	0	19	0	0	1	0	3	3
Proportion of cases which are ambulatory (%)	75	53	75	96	65	0	45	0	48	48
Proportion of cases which are hospitalizations (%)	25	47	25	4	35	100	55	100	52	52
Reported # of dengue cases per country (thousands)	387	11	8	2	44	11	31	81	27	323
Total annual number of ambulatory cases in public sector (thousands)	148	5.5	4.2	1.5	22	0	11	0	24	132
Total economic burden of ambulatory cases in public sector ($, millions)	43	0.49	0.37	0.5	3.7	0	3.6	0	6.5	12
Total annual number of ambulatory cases in private sector (thousands)	142	0.29	1.8	0.42	6.9	0	2.7	0	1.7	22
Total economic burden of ambulatory cases in private sector ($, millions)	41	0.03	0.16	0.14	1.2	0	0.84	0	0.33	1.4
Total annual number of hospitalization cases in public sector (thousands)	51	5.2	2	0.07	15	11	17	81	23	164
Total economic burden of hospitalization cases in public sector ($, millions)	34	2.3	0.83	0.07	9.7	1.3	16	46	14	22
Total annual number of hospitalization cases in private sector (thousands)	45	0	0	0.02	0	0	0.2	0	0.03	4.8
Total economic burden of hospitalization cases in private sector ($, millions)	31	0	0	0.02	0	0	0.2	0	0.02	1
Total combined economic burden for all cases ($, millions)	150	2.9	1.4	0.7	14	1.3	20	46	21	36

There is a small but viable travel market for dengue vaccines in developed countries (which overlaps with the market for yellow fever and Japanese encephalitis vaccines). We have assumed Sanofi will target this segment, but that the volume sold will constitute a small proportion of production (10%). Sanofi will be subject to substantial community pressure to sell most of its vaccine in lower and middle income countries. Pricing of dengue vaccines is very unlikely to be determined by the free market. Rather, it will be determined through negotiation with key national governments, and this will set a benchmark that other countries will follow (as was the case with GSK's pneumococcal vaccine, Moon et al., 2011). National governments will demand a price that is affordable. We assume that Sanofi will act in a rational manner and agree to a price that allows all of its volume to be sold, since artificial restriction of supply below 100 million doses will not increase prices but will be associated with substantial negative community pressure.

Production costing of the future Butanten-NIH-licensed vaccine plant has been based on a 60 million dose capacity (Mahoney et al., 2012). The planned capacity of other plants is not known. In the absence of more specific information, the most reasonable assumption is that capacity will be equivalent or below that of the Sanofi plant (100 million doses annually).

We assumed a vulnerable population at 3.0 billion (with a range from 2.5–3.5 billion), in 2009, with an average population growth rate of 1.02% and a mean lifespan of 71.9 years. These values represent a weighted average for the countries with the largest case loads per country (Brazil, Venezuela and Thailand, see Table 1) and the global average for the rest of the world (data for average lifespan and annual population growth from the World Bank, available at www.google.com/publicdata). Sanofi's vaccination schedule is known to be a three dose regimen (Sanofi, 2012). We have assumed, as have others (Amarasinghe and Mahoney, 2011) that 25% will be wasted. We assumed that some of the later vaccines may offer improvement terms of shortening of the vaccination schedule (to one or two doses). We predict that the efficacy of a dengue vaccine will be 81% (cumulative probability of an efficacy of 95% against all four serotypes). Finally, we predict, as others have assumed (Amarasinghe and Mahoney, 2011), that the pediatric market will be targeted first in developing countries as this is most cost effective from the customer (government) perspective, and additional capacity if available will be used for 'catch-up' vaccination. We have not explicitly included the possibility that catch-up vaccination might require fewer doses due to prior dengue exposure, as there are currently no clinical efficacy data for the dengue vaccines in development.

With these input assumptions, we performed 10,000 simulations to model the effect on the annual clinical case rate of dengue, and the cumulative proportion of the population unvaccinated from the year of introduction of the first dengue vaccine (2015) until eight years after the latest feasible introduction of a dengue drug currently in the discovery phase of development (2033). Based on precedent, eight years is the likely period during which premium pricing could be negotiated with national governments. The year by year projected clinical case load and cumulative proportion unvaccinated are presented in Figs. 1 and 2. We have presented the range of possible outcomes for these two variables in 2033 in Figs. 3 and 5, and corresponding variance analyses in Figs. 4 and 6.

Table 2
Weighted average economic burden of dengue per case (2006 US $) and weighted proportion of total cases for each market segment.

Treatment Setting	Average cost per case in Suaya et al. countries ($)	Weighted average cost per case including ROW ($)	Proportion of total cases (%)
Ambulatory public	269	204	33
Ambulatory private	283	215	27
Hospital public	609	462	32
Hospital private	677	514	8

Table 3
Global aggregate economic burden, pricing and spending on a dengue drug with various capacities to relieve the economic burden of dengue (all economic values in 2006 US $).

Economic burden relieved and associated pricing – Global Aggregate			
Estimated global aggregate annual cases in 2006			5.4 million
Estimated global total annual economic burden in 2006			$1.70 billion
Global average cost per case			$313
Proportion of economic burden relieved by new treatment to be spent on that treatment			50%
Parameter	Levels of reduction in cost		
	20% economic burden relieved	40% of economic burden relieved	60% of economic burden relieved
Economic burden relieved by new drug treatment ($, millions)	337	675	1013
Portion of economic relief to be spent on new drug treatment ($, millions)	169	338	506
Proposed price for new drug treatment ($)	31	63	94

Table 4
Assumptions for dengue vaccine impact calculations.

Assumptions	Most likely value	Distribution	Minimum value	Maximum value	Standard deviation or custom values
Probability of Sanofi vaccine approval	Yes = 1	Yes–No	0	1	75% yes, 25% no
Launch date of competitor vaccines	2019	Discrete uniform	2017	2021	NA
Susceptible population (millions)	3000	Triangular	2500	3500	NA
Number of additional vaccines	1	Custom discrete	0	6	19.2% 0, 35.7% 1, 28.5% 2, 12.63% 3, 3.36% 4, 0.54% 5,0.05% 6
Vaccine efficacy	81%	Minimum extreme	50%	95%	Scale 9%
Multiplier for unreported cases	6	Normal	4.15	7.85	0.6
Regimen (doses) for additional vaccines	3	Custom discrete	1	3	20% 1, 30% 2, 50% 3
Vaccine wastage	25%	Normal	17%	33%	2.5%
Proportion of cases in non-Suaya countries	.36	Normal	0.25	0.47	0.036
Market uptake of Sanofi vaccine each year	25%	Normal	17%	33%	2.5%
Market uptake of alternate vaccines per year	25%	Normal	17%	33%	2.5%
Average life expectancy in susceptible regions	71.9	Minimum extreme	60	78	Scale 3.6
Diversion of capacity to western markets	10%	Normal	7%	13%	1%
Population growth	1.02%	Normal	0.6%	1.5%	0.102%

2.3. Alternative pricing schemes and maximum potential market for dengue drugs

Pharmaceutical innovators require a period of market exclusivity after drug approval in order to recoup research and development costs. In industrialized countries, this is accomplished through patent protection, data exclusivity and/or an explicit market exclusivity period provided by statute. While many of these legal provisions exist in middle income countries (IFPMA, 2011), the perceived fairness of proposed pricing is an equally important consideration. Many countries have nationalized patents when the price of life-saving medications has been perceived to be excessive. Also, while some countries have legal capacity to allow a period of market exclusivity, there may not be an explicit requirement or mandated minimum period. Therefore, pricing of interventions that are considered in the vital national interest are likely to be based on negotiation with key regional governments, rather than set in the free market. (Brazil's recent pricing agreement with GSK for pneumococcal vaccine is an example of this). Our proposal is that the fairest way to negotiate premium pricing during a period of market exclusivity is on the basis of economic burden relieved.

A dengue drug has the potential to alleviate symptoms and prevent disease progression, and thereby decrease medical costs, and time away from work and school. Therefore, while interventions impose an economic burden, they offer a counterbalancing reduction in economic burden if priced appropriately. All the input economic costs of a disease and the degree to which an intervention relieves them are, in theory, measurable in clinical trials. The potential ranges of therapeutic effects of a dengue drug are 20–60% relief of symptoms which we have assumed will translate into an equivalent reduction in economic burden. From a practical standpoint, it would be difficult to demonstrate that the effect of a drug was statistically significant if its magnitude did not exceed 20%. This sets our floor. We selected an upper limit of 60% since there are very few drugs on the market that reduce symptoms in a treatment setting to that degree. We then determined the maximum potential value created by one or more dengue drugs that collectively capture 100% value over a range of possible effectiveness (Table 3) and the weighted average cost per case based on the input data in Table 2.

Assuming that there was consensus that drug pricing should be agreed on the basis of economic burden relieved during a temporary period of market exclusivity, it follows that the price negotiated would represent some fraction of the total aggregate costs of dengue on a country by country basis. In theory, a national government should be willing to pay a total aggregate cost for provision of a dengue drug that is $1 less than the economic costs saved by the same drug. In this situation, a national government would effectively save $1 to alleviate a defined percentage of morbidity and mortality associated with dengue. However, this is unlikely to be perceived as fair by sovereign governments or the public who have a more humanitarian view of the alleviation of morbidity and mortality. We propose that a more attractive approach to pricing for the purchasers might be to split the expected economic benefits created by a drug evenly between the supplier and the party realizing those economic benefits. A pricing strategy which allows the purchasers to realize a net economic savings will provide greater incentive for more rapid adoption of a newly licensed drug. We used this assumption as the basis of determining per case costs and the total market for dengue drugs globally and for several key national markets.

In developing our projections we have also made several other assumptions. To prevent inappropriate administration for non-dengue febrile illnesses and counterfeiting, we expect that a dengue drug would not be made available to patients outside of a health care setting where a diagnosis of dengue can be established. It is likely that most dengue patients that would desire a dengue drug would initially be seen either in an ambulatory setting such as a health clinic or in a hospital. We have based our pricing on the weighted average cost of dengue cases on a country by country basis, assuming that drug distribution would be through national Ministries of Health (MOHs) for all intra-country market segments.

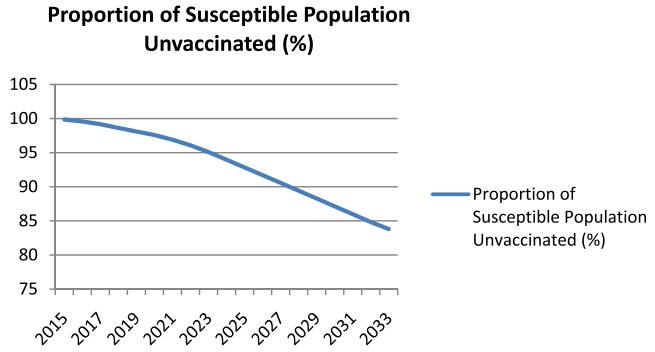

Fig. 1. Projected proportion (%) of susceptible population unvaccinated: 2015–2033. The horizontal access represents calendar year.

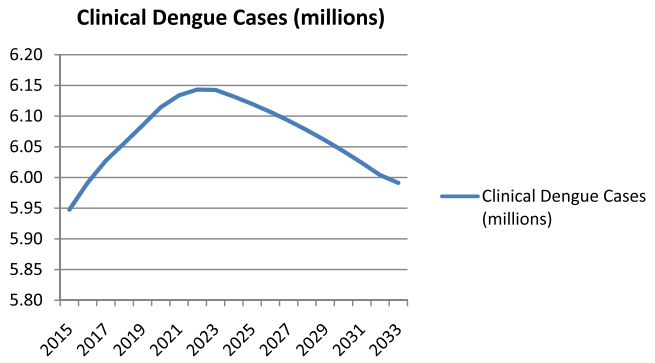

Fig. 2. Projected clinical dengue cases (millions): 2015–2033. The horizontal axis represents calendar years.

The vaccine impact modeling suggests that the annual clinical case load of dengue is not likely to decline between the introduction of a dengue vaccine (2015) and the end of a period of market exclusivity of eight years for a dengue drug licensed in 2025 (2033). Therefore, the maximum potential market for dengue drugs was based on the estimated dengue clinical case load used by Suaya et al., adjusted by a factor of 6 for unreported cases. The reader should note that our projections represent the maximum potential value of the entire market for dengue drugs during a period of market exclusivity. This does not mean that the entire value would be captured by the sales of one drug since there may be competitors, and no one drug may have the perfect profile to justify its use in all clinical settings.

3. Results

The total economic burden of dengue in each market segment that is presented in Table 1 for the eight countries examined by Suaya and colleagues. These were adjusted for unreported cases and other dengue markets not examined by Suaya et al., to yield a total economic burden of dengue is at least 2006 USD $1.69 billion annually (Table 3). Assuming dengue drugs had been available in 2006, and reduced 20%, 40% or 60% of costs, the total potential value created for patients and national governments would have been 2006 US $337, 676 and 1013 million respectively (Table 3). These values are relevant for the idealized case of a market with a single drug or multiple drugs during a period of market exclusivity and 100% value capture.

Dengue vaccination has the potential to dramatically reduce the number of clinical cases (and therefore the unmet medical need for a dengue drug) if it were possible to vaccinate a proportion of the population greater than that required for induction of herd immunity. Our projections suggest that even by 2033, under the likeliest circumstances, the majority of the susceptible population (84%) will remain unvaccinated (Fig. 1) and in 97.5% of our simulations the proportion unvaccinated exceeded 75% (Fig. 3). This suggests that herd immunity will not be reached globally prior to 2033, since this would require that 80–85% of the population be vaccinated.

The number of clinical cases is projected to peak in 2022 at 6.1 million per annum, but is projected to remain higher than 5.8 million cases throughout the period from 2015–2033 (Fig. 2). In 2033, the most likely scenario was 5.9 million clinical cases, with 97.5% of simulations resulting in 4.5 million cases per annum. For the proportion unvaccinated, the largest sources of variance were (i) the probability of the Sanofi vaccine achieving licensure,

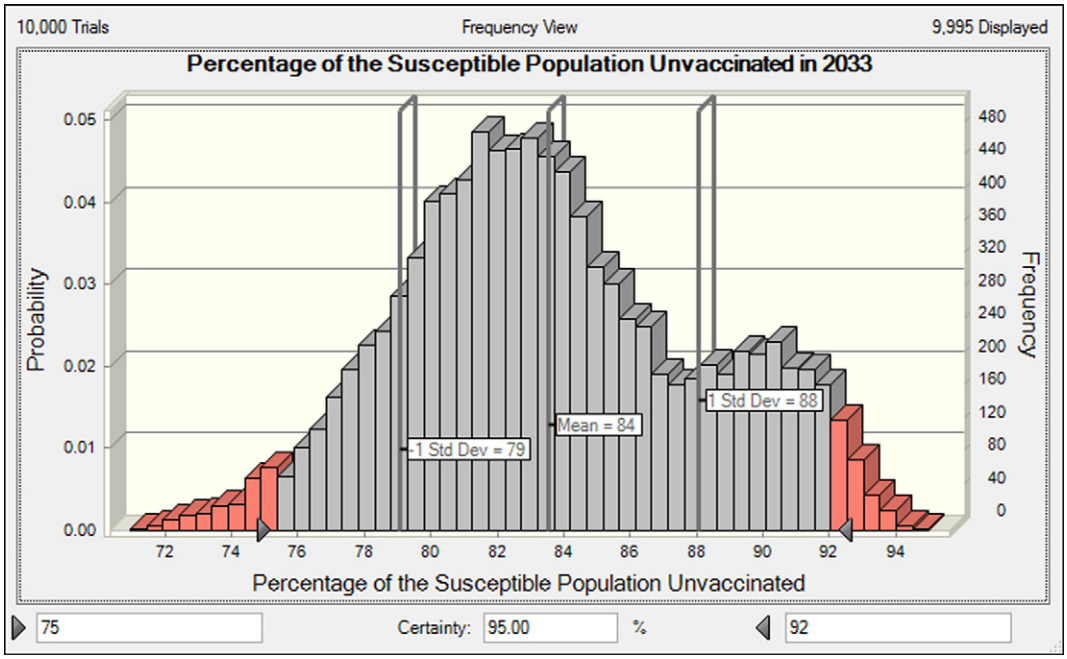

Fig. 3. Range of projected outcomes for susceptible population unvaccinated in 2033.

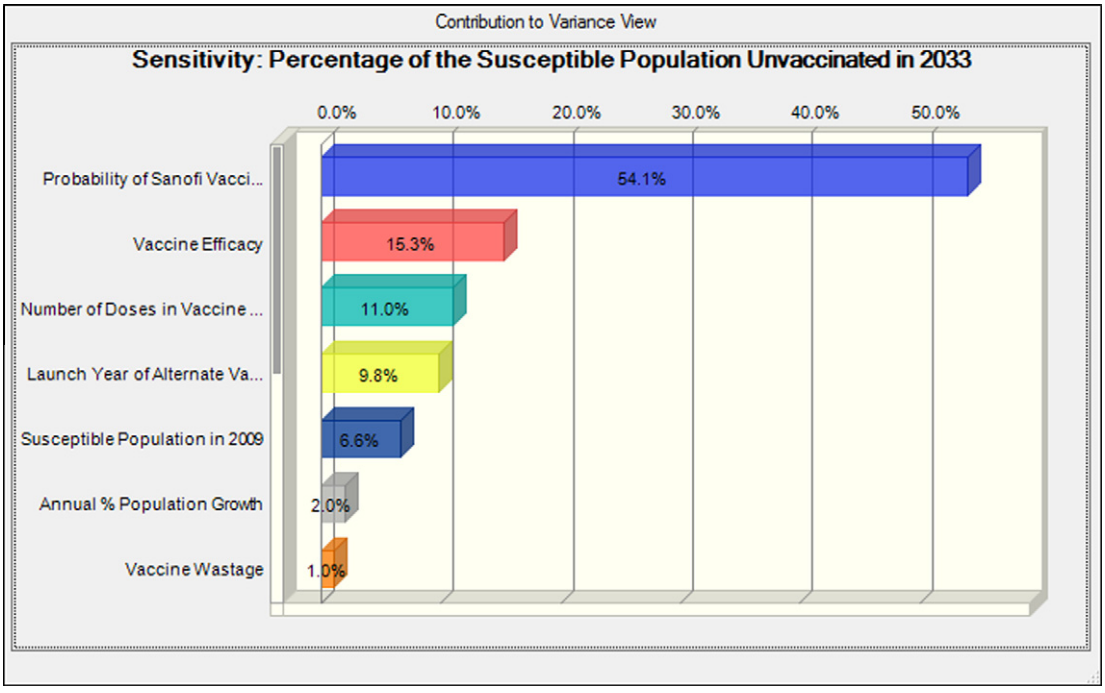

Fig. 4. Sources of variability in projected outcomes for susceptible population unvaccinated in 2033.

(ii) vaccine efficacy and (iii) number of doses of vaccine required to achieve the desired level of efficacy. For projected clinical cases, the largest sources of variance were (i) the multiplier for unreported cases, (ii) the proportion of dengue cases in non-Suaya countries and (iii) population growth. The implications of different assumptions regarding these sources of variance are discussed later.

The vaccine impact calculations suggest that the introduction of a dengue vaccine will not reduce the projected clinical case below 2006 levels in the short-medium term (through 2033). Effectively this means that the economic burden described here for dengue in 2006 will persist, and is not addressable by dengue vaccination unless there are major deviations from our current level of knowledge not factored into our simulations. However, this unmet medical need and economic burden is addressable with dengue drugs. Therefore, in the calculations for the size of the potential dengue drug market that follow, we have assumed a persisting annual economic burden of dengue equivalent to 2006. Presumably, in the absence of a dengue vaccine, the number of dengue cases would have continued to increase as a function of population growth (more susceptible individuals), increased urbanization (increased concentration of people with vectors) and climate change (expanded

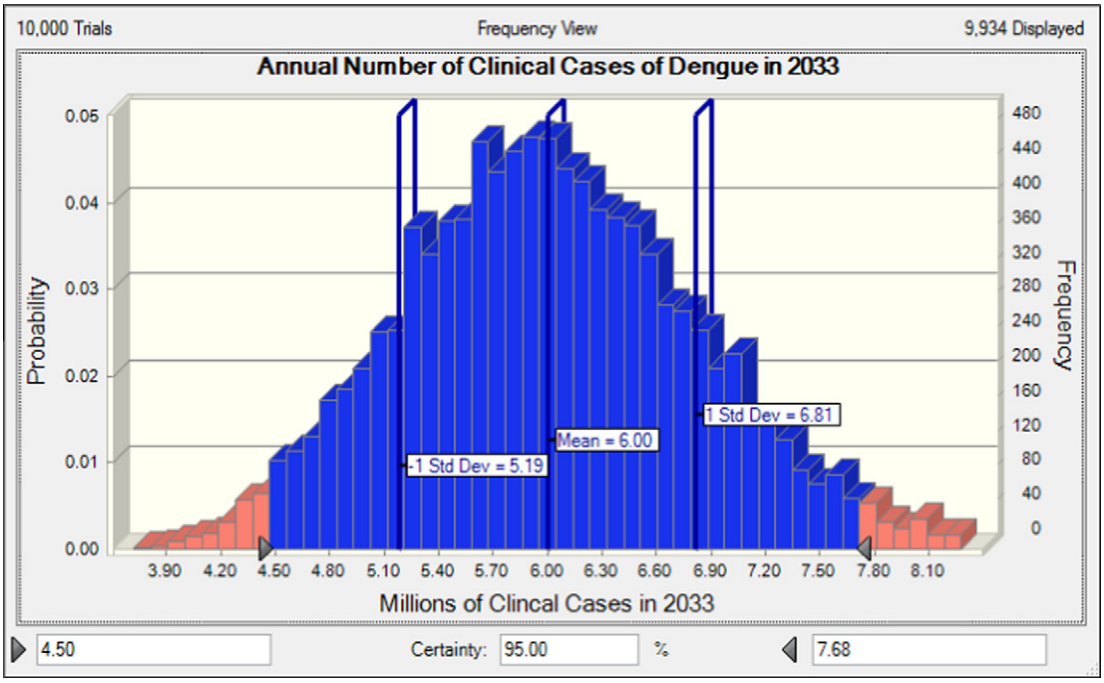

Fig. 5. Range of projected clinical cases (millions) in 2033.

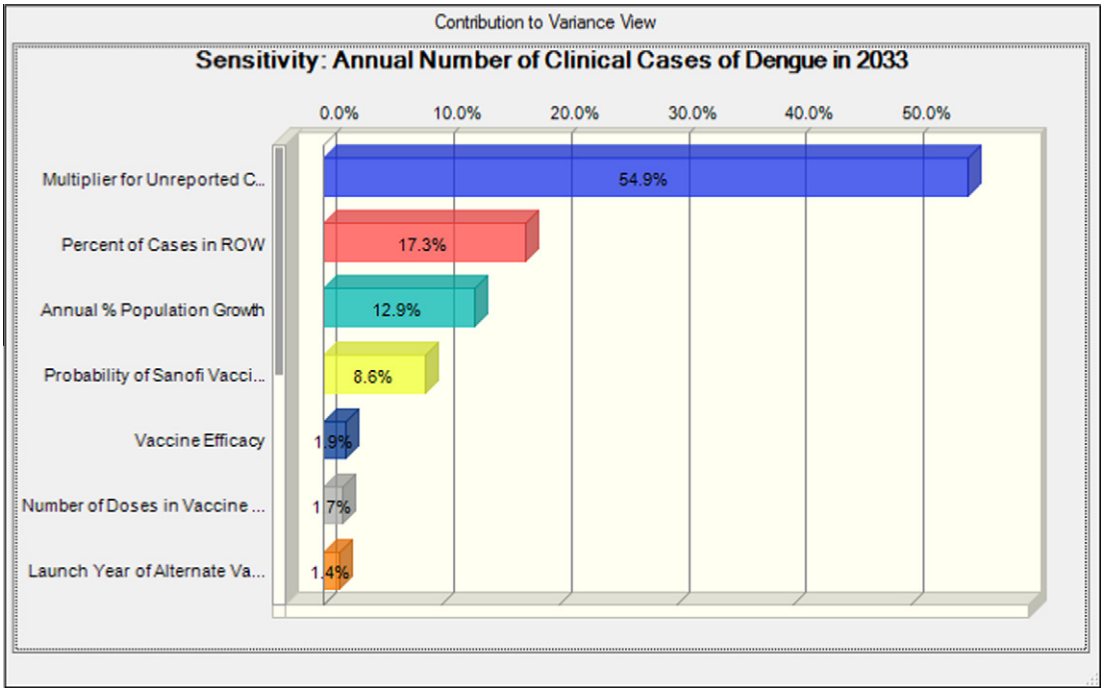

Fig. 6. Sources of variability in projected outcomes for projected clinical cases in 2033.

range of vectors). Our calculations explicitly do not address the economic burden that might be associated with this putative expansion in dengue cases that is preventable through vaccination.

Our proposal for tiered pricing is that during a negotiated period of market exclusivity, national governments would agree to pay an amount for an intervention that is equivalent to 50% of the economic burden relieved by that intervention. If this proposal were to become widely adopted, the maximum value of the potential market for dengue drugs annually would be 2006 US $169, 338 and 506 million if on average the available drugs reduced 20%, 40% or 60% of the economic burden of dengue respectively (Table 3). These figures might be lower if the period of market exclusivity of one or more innovator drugs had expired.

The price per course of treatment was calculated based using this model. For a drug that reduced 40% of economic costs, the weighted global average cost is $63 per treatment course (Table 3). Regional pricing would be $77, $115, $133 and $23 for Brazil, Thailand, Malaysia and Cambodia respectively (Table 5). Note that this is the total price for an effective treatment course of a dengue drug, NOT the expected price per pill.

4. Discussion

Dengue is classified as a neglected disease by the World Health Organization (WHO, 2012b). From the perspective of a pharmaceutical innovator, this implies that in aggregate the commercial market for drugs or vaccines for this disease might be small. For dengue drugs this is even more pertinent if dengue vaccines effectively induce herd immunity. As dengue drug discovery and development ratchets up over the next ten years it is essential to understand whether this reflexive assumption is true. If the estimate of the maximum size of the potential market for a dengue drug did not exceed the cost of development of even a single successful dengue drug (which in itself would be unlikely to capture 100% value), it follows that dengue drug development would be a financially futile endeavor or would require large government subsidies to be successful.

In order to arrive at such an estimate of the potential market for dengue drugs we have proposed solutions or simulations of three complex social, commercial and scientific problems: (i) estimation of the global economic burden of dengue, (ii) dengue vaccine impact calculations and (iii) an alternative to tiered drug pricing. We consider each of these solutions to represent Version 1.0. This is because we have made many assumptions where there may be limits to what is currently or publicly known, and/or we have made simplifications of evolutionary or economic dynamics out of necessity. In the next few paragraphs we have attempted to put some of these issues in context.

With respect to estimation of the global economic burden of dengue, we have assumed that the multiplier for unreported cases is 6, that the cases load of dengue outside those countries studied by Suaya et al. is 36%, and that the economic burden of dengue in those countries can be approximated based on GDP. Our model also incorporates the limitations of the input economic data generated by Suaya et al. the most important of which is that it is not known whether the experience of regional hospitals and medical clinics is representative of an entire country. The use of a multiplier for unreported cases is well established in the literature; indeed Suaya et al. (2009) utilized multipliers in initial projections of the regional economic burden of dengue. A multiplier of 6 for all dengue cases has been suggested, and this value is the approximate weighted average of conservative estimates of multipliers for hospitalizations (1.6) and ambulatory cases (10) assuming a 50:50 split in the case load (see summary in Suaya et al., 2009). Our assumption, that 36% of the dengue burden is represented by non-Suaya countries, reflects the best publicly available information, but will need to be adjusted in Version 2.0 if better estimates are forthcoming. Extrapolation of costs based on GDP is necessarily approximate, but is not unreasonable given relative medical and labor costs should be broadly reflective of differences in GDP.

With respect to vaccine impact calculations, the variables, other than the above, that contributed the greatest variance in our simulations were (i) the probability of approval of the Sanofi vaccine, (ii) vaccine efficacy, (iii) number of doses required for effectiveness and (iv) population growth. The Sanofi dengue vaccine is currently in Phase III. While much of the risk has been discharged, hurdles remain. These include meeting internal corporate targets for vaccine safety and efficacy, regulatory approval of the production process, regulatory approval of the clinical data package, and education on national governments of the benefits of a dengue vaccine versus the potential risk of antibody mediated enhancement and setting an appropriate price. The point is that the probability of success is not 100%. Since the dengue vaccine will protect people from four viruses, not one, it is unlikely that the efficacy of a dengue vaccine will be the same as vaccines for Japanese encephalitis and yellow fever (i.e. ~95%). The Sanofi vaccine is known to be a three dose regimen, but it is not yet known whether other vaccines will offer improvements. This is likely to be the case since it will offer a marketing advantage, however our assumed distribution reflects our perception that the bulk of regimens given will remain in the three dose format.

In the background to our dengue vaccine impact simulations we have included some necessary simplifications. For example, we have assumed that clinical case rates are related linearly to the absolute number of unvaccinated individuals, and ignored the possible interactions between different strains of dengue. It would be better to make such assumptions based on actual data, but this information either does not exist at a global level, or will not be known until many years after vaccine introduction. Others in the field making calculations about vaccine cost effectiveness have made similar assumptions out of necessity (Shepard et al., 2004). We have also assumed that the partial dengue immunity in the community is 'baked in' to 2006 reported dengue case rates, and have not factored this effect on the dengue vaccine regimen because there are no data. It is also possible that dengue vaccines may not offer life-long protection, but again, there are no data. These uncertainties highlight the fact that the introduction of dengue vaccines represents a vast evolutionary experiment for which we do not yet know the outcome.

We highlighted the challenges of tiered pricing earlier. The world community has a fundamental choice to make if a better balance is to be achieved between incentives and risk reduction for pharmaceutical innovators and greater access of patients to better drugs. It would be preferable if pharmaceutical companies were more transparent about true research and development costs and governments directly reimbursed the cost of development of a successful drug. Such an approach would obviate most of the requirement for temporary market exclusivity and facilitate greater competitiveness within a shorter duration of time after drug licensure. We would welcome such a development; however the political obstacles are likely to be challenging.

An alternative is that there is an agreed period of market exclusivity independent of traditional legal concepts centering on intellectual property (patents and data exclusivity) during which a company is able to charge premium pricing. This may have been the basis from which GSK negotiated pricing for the pneumococcal vaccine with the government of Brazil (Moon et al., 2011). In this scenario, GSK is currently able to charge a set a price for eight years in exchange for technology transfer to Brazil at the end of this period. Here we are going further in proposing that negotiated pricing should be based on the measurement of economic burden relieved, where an innovator company receives 50% of the economic burden relieved on a per case basis. Inherent in this assumption is that it will be more common that not in the future that pricing of drugs for neglected diseases during periods of market exclusivity will be determined through negotiation with ministries of health and sovereign governments, not by the free market. Of course it is also reasonable to assume that at the conclusion of a period of market exclusivity, prices would be set on the basis of generic competition in a free market.

From the perspective of potential customers, our proposed pricing (Table 5) seems appropriate given what is known about other drugs for neglected diseases. Our model generated a lower end price for a treatment course of $13.80 (Cambodia for a drug associated with 20% reduction in cost) versus an upper pricing limit for a drug that reduced costs by 60% of $239 (Malaysia, data not shown). Pricing is tiered in the sense that less developed countries such as Cambodia would pay less than middle income countries such as Brazil. However, the model is more calibrated than tradi-

Table 5
Economic burden, resources spent on, and prices for a drug that reduces dengue costs by 40% in Brazil, Thailand, Malaysia and Cambodia. Monetary values are in 2006 $ US.

Parameter	Market			
	Brazil	Thailand	Malaysia	Cambodia
Economic burden relieved by new drug treatment ($, millions)	360	111	49	3
Proportion of economic relief to be spent on new drug product ($, millions) and proportion of total global sales (%)	180 (50)	56 (16)	25 (7)	1.5
Price per case ($)	77	115	133	23

tional tiered pricing systems because not all middle income countries (for example Brazil versus Thailand) would pay the same price. The range of pricing is appropriately lower than the cost of generic liposomal amphotericin for visceral leishmaniasis ($250, Moon et al., 2011), and the annual cost of HIV drugs in sub-Saharan Africa (up to $1000, Moon et al., 2011), given that those diseases are more life-threatening. At the lower end ($13.80 in Cambodia), pricing compares favorably with that of antimalarial drugs (up to $4.30, Tren et al., 2011) in sub-Saharan Africa, especially when one considers that antimalarial drugs are heavily subsidized. It is also important to remember that the actual cost per tablet will be lower than this, since a multiple day course of treatment is likely to be needed for dengue. We also remind the reader that we calculated prices only for countries where the input costs of dengue have been published (i.e. Suaya et al., 2009).

If such a pricing scheme came to fruition, the maximum potential total market for a drug or drugs that on average reduced 40% of costs and that collectively captured 100% of value during a period of market exclusivity is $338 million annually. This would be likely to remain stable during the period of market exclusivity after the introduction of the first innovator drug (perhaps as early as 2020), since competing innovator companies will attempt to set prices of new drugs at similar relative levels to the first innovator compound. An innovator compound entering such a market might generate 2006 US $2703 million ($338 million * 8 years) assuming no competition. Since large pharmaceutical companies are willing to spend around 19% of revenue on research and development (Congressional Budget Office, 2006), it follows that a total research and development spend of $514 million to capture such revenues might be feasible ($2703 million * 19%). Since major pharmaceutical companies active in the neglected disease sector (e.g. GSK) have publicly stated that a profit margin of 5% of revenue might be acceptable in this space (compared to the normal industry average of 16%), it follows that the potential research and development spend might potentially be as high as $811 million ($2703 million * (19 + 11%)). This is substantially higher than the median cost of a Phase III development program (2000 US $62 million) and post licensure research and development costs (2000 US $140 million, Di Masi et al., 2003).

However, it is important to reiterate that a single drug will not capture the entirety of this potential market as revenues due to the combined effect of competition from other innovator compounds and the likelihood that a single drug would not be appropriate for or reach all patients. Further articulation of this point would require more detailed information about a specific proposed dengue drug and is beyond the scope of the present work. Also, the monetary size of the potential market will likely decline after the introduction of generic versions of the first innovator compound as prices fall due to competition. The potential market would also be lower if the impact of vaccines on clinical case loads is greater than our simulations suggest. On the other hand, our model does not include additional sources of revenue such as licensing fees from out of field indications (e.g. hepatitis C) or the priority review voucher, and excludes the potential increase in the market that would result from dengue vaccine failure or low vaccine uptake due to safety concerns regarding antibody-mediated enhancement.

On balance, and in spite of many uncertainties and gaps in the data, our findings suggest that the potential market for a dengue drug, in terms of both the monetary value of the market and the annual number of dengue cases, will remain sufficient to facilitate the introduction of one or more dengue drugs. We anticipate that this will complement the expected use of vaccines in combating the morbidity, mortality and economic burden of dengue in the future.

Acknowledgements

GSD is grateful to colleagues in the EMBA 11 cohort and faculty at the Robert H. Smith School of Business, University of Maryland, for helpful discussions to develop the business case for development of drugs for neglected diseases including dengue.

References

Amarasinghe, A., Mahoney, R.T., 2011. Estimating demand and supply of dengue vaccine in Brazil. Hum. Vaccine 7 (7), 776–780.
Armien, B., Suaya, J.A., Sah, B.K., Barvard, V., Marchena, L., Campos, C., Shepard, D.S., 2008. Clinical characteristics and national economic cost of the 2005 dengue epidemic in Panama. Am. J. Trop. Med. Hyg. 79, 364–371.
Beatty, M.E., Beutels, P., Meltzer, M.I., Shepard, D.S., Hombach, J., Hutubessy, R., Dessis, D., Coudeville, L., Dervaux, B., Wichmann, O., Margolis, H.S., Kuritsky, J.N., 2011. Health economics of dengue: a systematic literature review and expert panel's assessment. Am. J. Trop. Med. Hyg. 84 (3), 473–488.
Coller, B.G., Clements, D.E., Bett, A.J., Sagar, S.L., Ter Meulen, J.H., 2011. The development of recombinant subunit envelope-based vaccines to protect against dengue virus-induced disease. Vaccine 29 (42), 7267–7275.
Congressional Budget Office, 2006. Research and development in the pharmaceutical industry. Publication # 2859, Congress of the United States.
Danko, J.R., Beckett, C.G., Porter, K.R., 2011. Development of dengue DNA vaccines. Vaccine 29 (42), 7261–7266.
Di Masi, J.A., Hansen, R.W., Grabowski, H.G., 2003. The price of innovation: new estimates of drug development costs. J. Health Econ. 22, 151–185.
Durbin, A.P., Kirkpatrick, B.D., Pierce, K.K., Schmidt, A.C., Whitehead, S.S., 2011. Development and clinical evaluation of multiple investigational monovalent DENV vaccines to identify for inclusion in a live attenuated DENV vaccine. Vaccine 29 (42), 7242–7250.
Guy, B., Barrere, B., Malnowski, C., Saville, M., Teyssou, R., Lang, J., 2011. From research to phase III: preclinical, industrial and clinical development of the Sanofi Pasteur tetravalent dengue vaccine.. Vaccine 29, 5860–5868.
IFPMA, 2011. Data exclusivity: Encouraging the Development of New Medicines. IFPMA, Geneva.
Mahoney, R.T., Francis, D.P., Frazatti-Gallina, N.M., Precioso, A.R., Watier, P., Whitehead, P., Whitehead, S.S., 2012. Cost of production of live attenuated dengue vaccines: a case study of the Instituto Butanten, Sao Paulo, Brazil. Vaccine 30 (32), 4892–4896.
Moon, S., Jambert, E., Childs, M., von Schoen-Angerer, T., 2011. A win-win solution? A critical analysis of tiered pricing to improve access to medicines in developing countries. Globalization Health 7 (1), 39.
Osorio, J.E., Huange, C.Y.H., Kinney, R.M., Stinchcomb, X.X., 2011. Development of DENVax: A chmieric dengue-2 PDK-53-based tetravalent vaccine for protection against dengue fever. Vaccine 29 (42), 7251–7260.
Sanofi, 2009. Press release – May 12, 2009: Sanofi-Aventis builds a new plant vaccine manufacturing facility in France with an investment of 350 million Euros. Accessed 8/15/12 online at <http://www.sanofipasteur.com/EN/media/press-tool-kits/focus-on-dengue.html>.
Sanofi, 2012. Press release – July 25, 2012: Sanofi-Pasteur's dengue vaccine demonstrates proof of efficacy. <http://en.sanofi.com/Images/30784_20120725_SP-Dengue-vaccine_en.pdf> (accessed 8/15/12).

Shepard, D.S., Suaya, J.A., Halstead, S.B., Nathan, M.B., Gubler, D.J., Mahoney, R.T., Wang, D.N.C., Meltzer, M.I., 2004. Cost-effectiveness of a pediatric dengue vaccine. Vaccine 22 (9–10), 1275–1280.

Suaya, J.A., Shepard, D.S., Siqueirra, J.B., Martelli, C.T., Lum, L.C.S., Tan, L.H., Kongsin, S., Jiamton, S., Garrido, F., Montoya, R., Amien, B., Huy, R., Castillo, L., Caram, M., Sah, B.K., Sughayyar, R., Tyo, K.R., Halstead, S.B., 2009. Cost of dengue cases in eight countries in the Americas and Asia: a prospective Study. Am. J. Trop. Med. Hyg. 80 (5), 846–855.

TDR, 2009. Dengue: Guidelines for Diagnosis, Prevention, Treatment and Control. World Health Organization, Geneva.

Tren, R., Bate, R., Hess, K., Ayodele, T., Cudjoe, F., 2011. The Global Funds' Malaria Medicine Subsidy: A Nice Idea With Nasty Implications. Africa Fighting Malaria, Washington DC.

WHO, 2012. Fact Sheet 117: Dengue and severe dengue. <http://www.who.int/mediacentre/factsheets/fs117/en/> (accessed 3/22/12).

WHO, 2012b. Diseased covered by NTD department. <http://www.who.int/neglected_diseases/diseases/en/> (accessed 8/15/12).

Zemmel, R., Shiekh, M., 2010. Invention reinvented: McKinsey perspectives on pharmaceutical R&D. McKinsey and Company.