Disease Control Priorities Project

Working Paper No. 17
September 2003

Cost-Effectiveness of a Pediatric Dengue Vaccine

Donald S. Shepard, Ph.D.
Jose A. Suaya, M.D., M.B.A.
Scott B. Halstead, M.D.
Michael B. Nathan, Ph.D.
Duane J. Gubler, Sc.D.
Richard T. Mahoney, Ph.D.
Daniel N. C. Wang
Martin I. Meltzer, Ph.D.

Schneider Institute for Health Policy
Heller School, Room G19, Mail Stop 035
Brandeis University
Waltham, MA 02454-9110
Tel: 781-736-3975 • Fax: 781-736-3928
Web: http://www.sihp.brandeis.edu/shepard
E-mail: Shepard@Brandeis.edu

The Disease Control Priorities Project is a joint effort of The World Bank, the Fogarty International Center of the National Institutes of Health, the Bill & Melinda Gates Foundation, and the World Health Organization.

Cost-effectiveness of a Pediatric Dengue Vaccine

Donald S. Shepard, Ph.D.
Jose A. Suaya, M.D., M.B.A.
Scott B. Halstead, M.D.
Michael B. Nathan, Ph.D.
Duane J. Gubler, Sc.D.
Richard T. Mahoney, Ph.D.
Daniel N. C. Wang
Martin I. Meltzer, Ph.D.

Schneider Institute for Health Policy
Heller School, Room G19, Mail Stop 035
Brandeis University
Waltham, MA 02454-9110
Tel: 781-736-3975 • Fax: 781-736-3928
Web: http://www.sihp.brandeis.edu/shepard
E-mail: Shepard@Brandeis.edu

Length of summary, text, and acknowledgments: 4180 words

September 16, 2003

Forthcoming in Vaccine

Key words: dengue, vaccine, vaccination, cost-effectiveness, disability-adjusted life year, DALY, developing countries, cost, Southeast Asia.

Summary

To ascertain the economic feasibility of a pediatric tetravalent dengue vaccine, we developed and calibrated a cost-effectiveness model of vaccinating children at 15 months in SE Asia using a societal perspective. We assumed that full immunization would require two doses at prices of $0.50 and $10 each in the public and private sectors, respectively. The gross cost per 1000 population (of all ages) of the vaccination program would be US $154. Due to projected savings in dengue treatment, the net cost per capita would be only $17 (89% below the gross cost). The cost per disability adjusted life year (DALY) saved by a pediatric vaccine would be $50, making the potential vaccine highly cost-effective. Eventually, vaccination may be able to replace environmental control as a strategy for dengue prevention and be cost saving.

1. Introduction

Recent reports on dengue, a mosquito-borne disease which threatens half the world's population[1], have highlighted economic and financial issues as critical questions affecting completion of research, development and use of dengue vaccine. Epidemiological publications and surveillance reports have documented the sobering increase in cases and deaths from dengue[1] and its spread to new areas, such as the Middle East and the US states of Texas[2],[3] and Hawaii[3], thereby greatly increasing the importance of effective control programs. Furthermore, continued progress on vaccine development has increased the likelihood that an effective vaccine against dengue is technically possible[4]. Yet, as dengue is a tropical disease that threatens few industrialized countries, the vaccine may remain an orphan[5]. We suggest here, however, that the potential sales of a dengue vaccine would be sufficiently large in South East Asia to support reasonable development and production costs and yet make the vaccine available at an affordable price.

Periodically, economic analyses are conducted to guide public support for vaccine development in both industrialized[6] and developing[7],[8] countries, including a previous cost-effectiveness study of dengue[9]. Inadequate economic analysis may have delayed the adoption of Hepatitis B vaccine (HBV) in developing countries by a decade.

Assuming a pediatric dengue vaccine proves safe and effective, here we examine whether it would be economically viable. We focus specifically on the region of Southeast (SE) Asia, where the disease has its highest incidence, primarily strikes children[10], and has been the site of major epidemics in the past 20 years. Focusing specifically on SE Asia, this paper (1) estimates the health benefits of offering dengue vaccination to annual child cohorts in that region, (2) determines the annual cost of that strategy; and (3) projects potential revenues to vaccine producers from sale of a pediatric dengue vaccine[11]. Our analysis is designed to inform the many stakeholders in vaccine development. They include the recently formed Pediatric Dengue Vaccine Initiative (www.pdvi.org), national governments, donors, research institutes, vaccine producers, and financing intermediaries such as the Vaccine Fund, which supports the activities of the Global Alliance for Vaccines and Immunization (GAVI)[12]. The stakeholders interact because investment decisions by donors and producers on vaccine development depend, in part, on the potential utilization and revenue from a vaccine if it is developed.

2. Methods

We conducted this economic analysis using standard approaches to cost-effectiveness analysis[13],[14] to derive the cost per Disability Adjusted Life Year (DALY) saved[15]. Each DALY saved represents one year of healthy life gained due to postponement of mortality and/or reduction in rate or severity of morbidity. The ten countries in SE Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam) had a combined population in 1999 of 529 million persons[16]. From 1997 through 2001, these countries officially reported to the World Health Organization (WHO) 1.2 million cases of dengue fever (DF) or dengue hemorrhagic fever (DHF), a life-threatening form of the disease, while the actual burden is projected to be far higher[17]. Our target population, the cohort of 11.6 million children in SE Asia who reached the age of 15 months sometime in 2001, was based on births in 1999[18],[19].

Our time horizon for the analysis was the lifetime for the cohort, which was set to have a life expectancy equal to that in SE Asia (66 years). The estimated lifetime number of infections per person for SE Asia is 3.3[2]. Consequently, the expected average annual dengue infection rate is 5% overall (calculated as 3.3 lifetime infections per person divided by 66 years of life expectancy per person). Based on the concentration of infections in children, we estimated annual infection rates of 12.5% in children under 15 and 2.8% in adults. Although costs and health benefits will occur in the future, we expressed them in rates per 1000 persons in the 1999 population of SE Asia. We adopted a societal perspective for evaluating costs and benefits and used official exchange rates to convert foreign currencies to US dollars. We compared vaccination of the cohort against the current situation, i.e., no dengue vaccination exists and vector control programs attain moderate coverage and effectiveness throughout SE Asia. These vector control programs entail varying levels of public education, inspection of potential breeding sites, elimination or appropriate management of larval habitats, and insecticidal measures against larvae and adults.

Figure 1 portrays the current rates of disease progression without vaccination, based on available literature[10],[17],[20]. Based on these rates, we estimate that on average in SE Asia, 26 million infections occur in an average year, of which 6.3 million are clinically apparent. From them, 381,000 persons (mostly children) develop the serious and life-threatening complication, dengue hemorrhagic fever (DHF) or dengue shock syndrome (DSS), while 3,047 die annually. Drawing on experience from Thailand[20], we used age 8 as the average age of hospitalization and death from dengue, leading to a loss of 34 DALYs per dengue death [21]. We assumed an average duration of 5.5 days for DF (non-DHF) and 9 days for DHF and a quality of life during these episodes on a scale where 0 is equivalent to death and 1 to perfect health of 0.19 for DF (non-DHF) and 0.15 for DHF. The quality of life values were based on losses per day (compared to perfect health) of 0.81 and 0.85, respectively[17].

We estimated treatment costs (ambulatory visits, hospitalization, medications, travel expenses, and parents' time seeking treatment) from a detailed study in Thailand[20] and studies of hospital costs across several countries[22]. We adjusted for differences in wage rates and prices among countries in the region and over time by scaling treatment and control costs in proportion to Gross National Income (GNI) per capita[19] with a population-weighted average per capita GNI for SE Asia for 2001 of US $1083, giving a cost per case of $139 for DHF, $4.29 for DF (non-DHF), and $12.39 overall (DF or DHF).

Figure 1 also serves as the basis for our model of vaccination, where each oval represents a model state and each arrow the most likely percentage of subjects progressing to the next state over the course of his dengue infection. Sensitivity analyses below will consider alternative assumptions. As all subjects face the same proportions and there are no differences by gender, our model is deterministic. Under our model, vaccination would affect only the 5% annual rate from "population" to "infection". In consultation with dengue experts at a major international meeting[23] and based on experience with other vaccines, we assumed that vaccination would be 95% efficacious in providing lifetime protection against each of the four dengue virus serotypes, reducing the recipient's annual risk of infection to 0.25%. Vaccination would have negligible side effects.

We assumed that children would be vaccinated with two doses. We projected a mixed distribution system (both public and private) and two-tiered prices from experience with HBV. For children vaccinated in public sector, the first dose would coincide with the visit for measles vaccination, generally given at the average age of 9 to 12 months[3]. The second, requiring a separate visit, would occur around 18 months, the age just prior to the period of risk. For children vaccinated in the private sector, we assumed that neither dose would coincide with an existing vaccination and each thus dose would require a separate visit. Based on the current vaccination coverage for DPT3 in SE Asia, we assumed that 85% coverage would be achieved at full implementation, and additional doses would be procured to compensate for an estimated 20% wastage rate[24].

We projected that the public sector would serve 90% of recipients and will procure the vaccine at $0.50 per dose. This is twice the price that the Vaccine Fund pays for HBV, and a fifth more than PAHO pays for the median recommended vaccine in the Expanded Program on Immunization[25]. The projected coverage assumes that the Vaccine Fund or other international institutions would help purchase doses of a dengue vaccine, once approved, in the poorest countries as they do currently for existing vaccines. For the remaining 10% of recipients (primarily middle and upper class children), we assumed that the vaccine would be delivered through the private sector at a procurement price of $10 per dose. These public and private prices cover the supplier's cost of production, amortized development, and profit. Immunological, epidemiological, economic, and effectiveness studies by the Pediatric Dengue Vaccine Initiative supported by grants from the Bill and Melinda Gates Foundation and other donors [26-28] are expected reduce risk and associated development cost to the suppliers. Syringes would cost $0.05 each. Costs per contact of labor, overhead, vaccine distribution, and storage for administering the vaccine would be $3.50 in the public sector based on other vaccination programs[8] and were assumed to be twice as much ($7) in the private sector. The model “discounted” health benefits (expressed as DALYs) and costs saved from vaccination at an annual real (net of inflation) rate of 3% per year.

To estimate revenue to vaccine producers, we made conservative assumptions. First, 8 years of further development are required with no revenues; then 5 years of partial revenue occur as coverage increases linearly up to 85%; finally 8 years of full revenues are realized; no further revenues are obtained, as the product becomes obsolete. We used a commercial cost of capital of 15% per year (12% net of inflation) and performed all calculations in Microsoft Excel XP®. Due to lack of evidence, our model did not include potential indirect benefits of vaccination, such as those from increased tourism, reduction of psychological fear by the public, and positive externalities to unvaccinated subjects from lowered dengue transmission due to fewer susceptibles in the population.

We performed sensitivity analyses of key variables and assumptions. First, we varied the public sector procurement price per dose over the range of $0.25 (the current price of HBV under the Vaccine Fund) to $1.50 (the price at which HBV started to be used in the public sector in developing countries)[11]. Second, we considered combination vaccines against dengue and other diseases, as recently occurred for HBV and Hemophilus influenza B (Hib) vaccines. Third, we varied the rate of clinical disease above and below our best estimate based on alternative values of Gubler and Meltzer’s[17] “multiplier” that projects actual cases from reported cases. For children under age 15, the age group experiencing the most dengue cases in our model, their “Method A” relying particularly on data from Thailand, estimated that the most likely value of the multiplier was 19, with a 95 percent confidence interval of 2 to 43[29-31]. Fourth, we considered a vaccine that provided only 10 years of protection. Fifth, we also examined a “least cost-effective scenario” with the lowest infection rate, a low vaccine efficacy (85%), the highest public sector vaccine price ($1.50), and only 85% of children served through the public sector. Sixth, we examined the actual mortality rates and life expectancy in SE Asia to translate deaths averted into DALYs, rather than the optimum mortality rates and life expectancy (model life table West level 26 , based on Japan) that are standard in DALY calculations worldwide[21]. Seventh, we examined the lowest coverage rate reported from SE Asia (70%, based on measles vaccination rates in Indonesia, Laos, and the Philippines)[32]. We assumed, however, that costs per contact would not vary with lower coverage levels.

3. Results

The baseline disease burden of dengue in SE Asia for the cohort is 0.42 DALYs per 1000 population, of which 52% is due to premature mortality and 48% to acute morbidity. The baseline cost of treatment is $99 per 1000 population per year. Although DHF constitutes only 6% of clinical cases, it represents 68% of the disease burden and 67% of the treatment costs.

Under our most likely assumptions, vaccination reduces both the mortality and morbidity burdens of disease by 82%, saving 0.34 DALYs per 1000 population per year. The incremental cost of vaccinating one child against dengue would be $4.85 in the public sector, $39.10 in the private sector, and $8.28 overall. Since each child would receive two doses, the cost per dose would be $4.14. The gross cost per 1000 population of the vaccination program would be $154.

This cost is relatively low because children must be vaccinated during just one year of their life, but that cost is allocated over the entire population. The net cost per 1000 population, $17, is 89% below the gross cost because of the savings in health care costs from fewer dengue cases. In aggregate, when fully implemented in SE Asia, dengue vaccination would cost $81.7 million per year, save $72.7 million in treatment, and have a net cost of $9.0 million. It would save 182,000 DALYs per year.

The dengue vaccination program would cost $50 per DALY saved. This cost-effectiveness ratio is the cost to buy a year of good health. The lower that ratio, the more favorable the health intervention. The calculated ratio also means that each $1 million invested in dengue vaccination would save 20,000 DALYs.

At full implementation, the vaccine sales for SE Asia for each annual cohort of infants would be 25 million doses and revenues would be $36 million per year, of which the private sector represents 10% of the doses and 69% of the revenues. The present value of revenues until the vaccine's obsolescence would be $66 million at the 15% nominal (or 12% real) commercial discount rate, but would rise to $228 million at the 6% nominal (3% real) discount rate used in public sector analyses[15].

4. Discussion

4.1 Burden of disease. The health burden of dengue estimated in this study (0.42 DALYs per 1000 population) is comparable to that of meningitis (0.39 DALYs per 1000 population) in the WHO region (Western Pacific) that includes most (7 out of 10) of the countries examined. It is twice the burden of hepatitis B (0.24 DALYs per 1000 population) and one third the burden of HIV-AIDS (1.16 DALYs per 1000 population), one of the major worldwide health threats[33]. In terms of economic burden, the cost per case of DF or DHF ($12.39) exceeds the comparably calculated cost per case of treating malaria of $9.14 to $9.22, based on costs from Burkina Faso[34] and Rwanda[35], respectively.

4.2 Cost-effectiveness. Cost-effectiveness interpretations should first relate to other health interventions as a whole. The cost-effectiveness ratio for a dengue vaccine in SE Asia ($50 per DALY saved) is comparable to the most favorable public health programs for children, which each cost less than $100 per DALY saved (i.e., control of respiratory infections, perinatal conditions, diarrheal disease, pertussis, polio, measles, tetanus, malaria, malnutrition, and vitamin A deficiency). It is 20 times more favorable than the treatment of leukemia[15].

Next, a dengue vaccine should be judged against other approaches to prevention, particularly environmental control. By contrast to the cost per DALY of $50 for vaccination, the published cost-effectiveness ratio for an environmental management approach to dengue prevention and control ($3,139 per DALY), derived from the Singapore experience, was far less favorable[9]. While a pediatric dengue vaccine would be expected to confer virtual lifelong immunity, environmental management, must be delivered repeatedly each year to the entire population as part of an integrated vector control strategy, with associated high recurrent costs. With few exceptions, sustained control or prevention of dengue virus transmission by vector control has not been achieved in recent decades, mainly due to operational constraints including weaknesses of program delivery, continuity and coverage, and over-reliance on insecticidal control methods, especially those targeting adult mosquitoes. Control programs have generally failed to engage communities in sustainable behavior change that prevents the creation of, or controls larval habitats.

We estimate that after many cohorts have been vaccinated, vaccinations would be at least as effective as current vector control programs, and could supplant them for purposes of preventing dengue transmission. To estimate the potential savings, we assembled the most recent available data on dengue vector control. As dengue is primarily an urban disease, more urbanized countries had higher spending. Annual cost per 1000 population was $15 in Indonesia (1998), $81 and $188 in Thailand (1994[20] and 1998, respectively), $240 in Malaysia (2002), and $2400 in Singapore (2000) (unpublished data, World Health Organization for Indonesia and Thailand; Ministry of Health, Malaysia; Ministry of the Environment, Singapore). For 1997, among 14 Latin American countries, corresponding spending on control ranged from $20 to $3560 with a median $260[36]. For 17 Caribbean islands in 1990, the corresponding expenditure ranged from $140 to $8,490 with a median of $1,340[37]. As control costs were predominantly for personnel, we used the same methodology applied for vaccination costs to compute the average expenditure on environmental control for SE Asia. In 2001 prices, this unweighted average was $66 per 1000 population. Thus, if vaccination allowed at least a one third reduction in spending on environmental control, it would be cost saving.

4.3 Vaccination costs. One of the most critical questions in pharmaco-economics concerns the price of the product. That price must satisfy the opposing needs of the consumers and the producers of a product. It must be high enough to satisfy the needs of the producer. That is, it must cover at least the amortized development and production costs plus a return competitive with other alternatives. On the other hand, it must be low enough that the public sector could purchase the vaccine on a large scale. This analysis for SE Asia suggested that our base case price per dose ($0.50 in public sector and $10 in private sector) could meet these two objectives. The proposed public price exceeds the cost per dose of older vaccines in the Expanded Programme on Immunization, but is below the price of the most recently introduced (e.g. HBV and Hib), suggesting it is a plausible average over the vaccine's anticipated lifetime. The hypothesized private price is comparable to existing private sector prices in SE Asia (e.g. $9.51 per dose for Hib and $13.59 for the Japanese encephalitis in Malaysia manufactured by Biken, J. Cardosa, private communication, June 2003). Both industry and government representatives at a major dengue conference understood the rationale for two-tiered prices of these magnitudes[23]. Under a national program, governments would purchase vaccines from producer via tender, with negligible commissions and fees.

The full cost per dose (weighted average of the public and private sectors, including labor and overhead) of $4.14 lies within the range ($0.50 to $6.00) of reported cost per dose in a systematic review of studies of expanding vaccination coverage[38]. Combination vaccines would have only negligible cost on the overall cost of vaccination based on the experience of the PAHO revolving fund in procuring a pentavalent vaccine (DPT, HBV, Hib), where the cost of the combined vaccine was slightly more than the sum of the components[19].

4.4 Limitations and results of sensitivity analyses. The greatest limitations in our model are uncertainties in its parameters. Multivalent vaccines have not yet reached the level of development to know their efficacy, duration and type of protection, and side effects. Incomplete reporting leads to uncertainty about the current burden of dengue. Our sensitivity analysis showed that even with less favorable vaccine performance and disease incidence, vaccination remained cost-effective. If the vaccine provided only 10 years of protection and no booster dose were available or administered, the vaccine's impact would be 62% less, net costs would be 6 times as high than the values with lifetime protection (because less treatment cost is averted) and the cost-effectiveness ratio would be $788 per DALY. Even under the least cost-effective scenario, the cost-effectiveness ratio of $960 per DALY is still less than the per capita GNI of Southeast Asia.

Sensitivity analyses showed that the two factors that most affected the cost-effectiveness of a dengue vaccine were: (1) the price per dose of vaccine and (2) the incidence of DHF. The base case values for this sensitivity analysis are bolded in Table 1. The low incidence of DHF (36 per 100,000 population per year) corresponds to half of the base case values for each age group, with an overall annual infection rate of 2.5%. The intermediate value (72) corresponds to the central values described in Figure 1. The high incidence (108) corresponds to an infection rate of 6% (16% for those under 15 years, and 3% for those 15 and above) and 30% of infections being clinical cases. Higher rates of infection would be impossible over the long run, as they would require reinfections with the same serotype. If the incidence of DHF were high enough and the price were low enough, savings in treatment of DF and DHF would more than offset the costs of vaccination. With the highest incidence of DHF, vaccination is actually cost saving (CS) for all four prices shown and, in fact, for any price per dose up to $1.73. The highest incidence and lowest price achieve the greatest savings. The cost-effectiveness ratio under least favorable assumptions in Table 1 ($683 per DALY) and the cost-effectiveness ratios for poorer vaccine performance ($788 and $960 per DALY) all fall in the same category as several other public health programs in adults (e.g. control of diabetes and motor vehicle injuries)[15]. Moreover, these cost-effectiveness ratios are less than the region's per capita GNI ($1083), another benchmark for cost-effective interventions. When applying the life table for SE Asia, 3.4% fewer DALYs were gained, so the cost-effectiveness rose slightly to $51 per DALY saved. The lower coverage of 70% does not affect the cost-effectiveness ratio because both vaccination costs and offsets in treatment of dengue are reduced proportionately.

4.5 Extension to other regions and population groups. The cost-effectiveness of vaccinations, like that of other preventive programs, is roughly proportional to the disease burden. While dengue has been endemic in Southeast Asia for decades, it returned to the Americas in 1980 and spread in Brazil, Venezuela, Mexico, and other countries. In the United States, 102 cases of DF were reported from Hawaii in 2001, the first outbreak on that island in 56 years[3]. Undoubtedly, the Americas would also want to use a dengue vaccine when available, as that region has higher per capita income than SE Asia and has operated highly successful vaccination programs. Extending vaccination to other regions, older children and adults in SE Asia (not included in annual cohorts in our model), travelers, and members of the military would increase vaccine sales and revenues substantially.

5. Conclusions

Several factors contributed to results favoring the development and subsequent use of a dengue vaccine. First, at a projected price of $0.50 per dose in the public sector, the dengue vaccine would be relatively inexpensive. This projection was based the recent success of large public sector procurement through the Vaccine Fund in driving down the price of HBV to half of this level. It also counted on donor involvement in effectiveness testing, large public sector procurement, with concomitant low marketing overhead, to provide the producer with a means to reduce unit costs of production and distribution, thereby increasing overall profitability. Second, by assuming that dengue vaccination would be linked with the last dose of the Expanded Program on Immunization, a high (85%) coverage rate seemed reasonable. Third, the study focused on SE Asia, the region of the world with the highest incidence of DF and DHF.

The distributional implications of vaccination (disease avoidance and cost incidence) are also favorable. Benefits are widespread. Without vaccination, each person would expect 0.8 clinical dengue cases over his lifetime; as vaccination reduces this incidence by 81%, almost everyone receives at least a moderate benefit by avoiding an acute painful illness. Vaccinees benefit most during childhood, since the incidence is highest during this period, but continue to avoid some dengue infections and cases during adulthood. Costs are distributed roughly by ability to pay. Vaccinating 90% of the population through the public sector at public expense, the vaccine will be widely available to all, and especially convenient to the 10% of the population voluntarily choosing the private sector. As a pediatric dengue vaccine would be highly cost-effective and broadly beneficial once developed, continued development and widespread use, once an effective product is made, deserve high priorities.

Acknowledgments

For constructive comments, the authors gratefully thank Jane Cardosa and members of the Pharmaco-economics working group at the Conference on Accelerating the Development and Introduction of a Dengue Vaccine for Poor Children, Ho Chi Minh City, Vietnam, December 5-8, 2001, whose travel was supported by The Rockefeller Foundation. In addition to the authors, its members were: John Aaskov, Jeffrey Almond, Don L. Douglas, Bruce Innis, Andrew MacKnight, and Ooi Eng-Eong. The authors also thank Clare L. Hurley for editorial assistance.

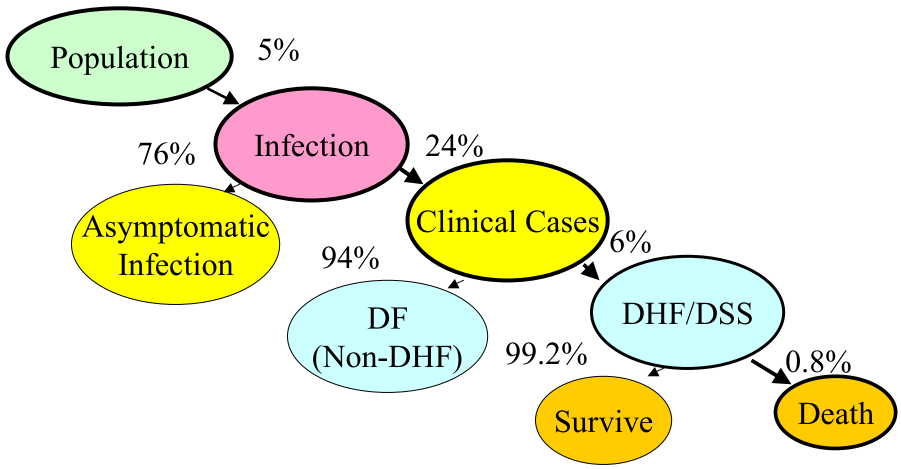

Figure 1. Rates in Dengue Model

Table 1.
Sensitivity Analysis: Impact of DHF Rates and Public Sector Cost of Vaccine on Cost-Effectiveness (US$/DALY Gained)

DHF per 100,000 Pop.	Public Sector Vaccine Price per Dose $ 0.25	**$ 0.50**	$ 1.00	$ 1.50
36	$438	$499	$622	$683
72	$19	**$50**	$111	$141
108	CS	CS	CS	CS

* CS denotes cost saving (i.e., vaccination costs less than the status quo).

References

1 Strobel, M. & Lamaury, I. Dengue fever: a review. *Rev Med Interne* 2001, **22**(7), 638-647.

2 Gubler, D.J. Dengue and dengue hemorrhagic fever. *Clinical Microbiology Reviews* 1998, (July), 480-496.

3 Centers for Disease Control. Notice: dengue fever in Hawaii. CDC. Accessed: January 23, 2002. http://www.cdc.gov/travel/other/dengue-hawaii-oct2001.htm

4 Kinney, R.M. & Huang, C.Y. Development of new vaccines against dengue fever and Japanese encephalitis. *Intervirology* 2001, **44**(2-3), 176-197.

5 Wilde, H. What are today's orphaned vaccines? *Clin Infect Dis* 2001, **33**(5), 648-650.

6 Stratton, K., Durch, J.S. & Lawrence, R.S., (eds). *Vaccines for the 21st Century: A tool for decision making.*, National Academy Press, Washington DC, 2001.

7 Institute of Medicine. *New vaccine development: establishing priorities; Volume II: Diseases of importance in developing countries*, National Academy Press, Washington, DC, 1986.

8 Shepard, D., Walsh, J., Kleinau, E., Stansfield, S. & Bhalotra, S. Setting priorities for the Children's Vaccine Initiative: a cost-effectiveness approach. *Vaccine* 1995, **13**(8), 707-714.

9 Shepard, D.S. & Halstead, S.B. Dengue (with notes on yellow fever and Japanese encephalitis). In *Disease control priorities in developing countries* (Eds. Jamison DT, Mosley WH, Measham AR & Bobadilla JL) The World Bank, Oxford University Press, New York, 1993. 303-320.

10 World Health Organization (WHO). *Dengue hemorrhagic fever. Diagnosis, treatment, prevention and control*, World Health Organization, Geneva, 1997.

11 Mahoney, R.T. & Maynard, J.E. The introduction of new vaccines into developing countries. *Vaccine* 1999, **17**(7-8), 646-652.

12 Global Alliance for Vaccines and Immunizations. Accessed: January 29, 2002. http://www.vaccinealliance.org/

13 Shepard, D. & Thompson, M. First principles in cost-effectiveness analysis in health. *Public Health Reports* 1979, **94**(6), 535-543.

14 Gold, M.R., Siegel, J.E., Russell, L.B. & Weinstein, M.C. *Cost-effectiveness in health and medicine*, Oxford University Press, New York, 1996.

15 World Bank. *World development report. Investing in health*, World Bank, New York, 1993.

16 Population Reference Bureau. Accessed: August 18, 2001. http://www.prb.org/Content/NavigationMenu/Other_reports/2000-2002/sheet1.html

17 Gubler, D. & Meltzer, M. Impact of dengue/dengue hemorrhagic fever on the developing world. *Advances in Virus Research* 1999, (53), 35-70.

18 United Nations. Expected births for 2001. Statistics Division. Accessed: January 29, 2002, 2000. http://unstats.un.org/cgi-bin/cdbdemo.exe

19 United Nations. Social indicators. Statistics Division. Accessed: January 29, 2002, 2001. http://www.un.org/depts/unsd/social/population.htm

20 Sornmani, S. & Okanurak, K. *Social and economic impact of dengue haemorrhagic fever in Thailand*, Social and Economic Units , Faculty of Tropical Medicine Mahidol University, 1995.

21 Murray, C.J.L. Quantifying the burden of disease: the technical basis for disabled-adjusted life years. *Bull World Health Organ* 1994, **72**, 429-445.

22 Shepard, D., Hodgkin, D. & Anthony, Y. *Analysis of hospital costs: a manual for managers.*, Geneva: World Health Organization, 2000.

23 Almond, J., Clemens, J., Engers, H. *et al.* Accelerating the development and introduction of a dengue vaccine for poor children, 5-8 December 2001, Ho Chi Minh City, VietNam. *Vaccine* 2002, **20**(25-26), 3043-3046.

24 UNICEF. The state of the world's children. Accessed: January 29, 2002, 1998. http://www.unicef.org/sowc98/tab1.htm

25 Pan American Health Organization (PAHO). Making vaccines affordable: revolving fund of the PAHO for vaccine procurement. Accessed: December 14, 2002, 2001. http://www.paho.org/English/HVP/HVI/revol_fund.htm

26 Pediatric Dengue Vaccine Initiative (PDVI). Objectives of PDVI. Accessed: December 14, 2002, 2002. http://www.pdvi.org/objectives

27 Halstead, S.B. & Deen, J. The future of dengue vaccines. *Lancet* 2002, **360**(9341), 1243-1245.

28 Chase, M. Research on dengue vaccine gets a $55 million foundation grant. in *Wall Street Journal*, New York, 2003. Sept. 10, p. D13.

29 Meltzer, M.I., Rigau-Perez, J.G., Clark, G.C., Reiter, P. & Gubler, D.J. Using DALYs to assess the economic impact of dengue in Puerto Rico: 1984-1994. *Am J Trop Med Hyg* 1998, **59**, 265-271.

30 Halstead, S.B. Dengue hemorrhagic fever - a public health problem and a field for research. *Bulletin of the World Health Organization* 1980, **58**, 1-21.

31 Burke, D.S., Nisalak, A., Johnson, D.E. & Scott, R.M. A prospective study of dengue infections in Bangkok. *AM J Trop Med Hyg* 1988, **38**, 172-180.

32 United Nations Department of Economic and Social Affairs. Millenium Indicators, Country Profiles. Statistics Division. Accessed: July 5, 2003. http://unstats.un.org/unsd/minew/mi.aspx

33 WHO. *The world health report 2002: Reducing risks, promoting healthy life.*, World Health Organization, Geneva, Switzerland, 2002.

34 Sauerborn, R.D., Shepard, D.S., Ettling, M.B., Brinkmann, U., Nougtera, A. & Diesfeld, H., J. Estimating the direct and indirect economic costs of malaria in a rural district of Burkina Faso. *Tropical Med, and Parasit.* 1991, **42**(3,Suppl I), 219-223.

35 Ettling, M. & Shepard, D. Economic cost of malaria in Rwanda. *Tropical Medicine and Parasitology* 1991, **42**(3,Suppl I), 214-218.

36 Pan American Health Organization (PAHO). A blueprint for action for the next generation: dengue prevention and control. Accessed: January 29, 2002, 1999. http://www.paho.org/English/HCP/HCT/hct-136-99.doc

37 Nathan, M.B. Critical review of Aedes aegypti control programs in the Caribbean and selected neighboring countries. *Journal of the American Mosquito Control Association* 1993, **9**(1), 1-7.

38 Pegurri, E., Fox-Rushby, J.A. & Damian, W. The effects and costs of expanding the coverage of immunisation services in developing countries: A systematic literature review. *Vaccine* in press.