A Technical Guide to using the Malaria Vaccine Spreadsheet

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TABLE OF CONTENTS

	27	tb children	91	Calculation of lifetime burden of tuberculosis for each child in a country
	28	tb old cohorts	91	Calculation of lifetime burden of tuberculosis for each pregnant woman in a country
	29	DPT3	82	2001 DPT3 takeup rate data
	30	coverage	93	Coverage rates in each country
results	31	timepath	94	Total # of people vaccinated, Cost/DALY
	32	revenues	96	Revenues to developer
GUI	33	GUI defaults	97	Default values of user-defined parameters
	34	helptexts	98	Help texts for GUI
	35	GUI	99	Contains the GUI
	36	GUI results	100	Contains the GUI outputs

INTRODUCTION

The vaccine calculations spreadsheet (Vaccine_spreadsheet.xls) can be used to estimate the cost effectiveness of a commitment to guarantee an initial high price for a malaria vaccine with specified characteristics.

The spreadsheet's many input parameters and specifications—which any user may change—enhance the flexibility of the analysis. For example, the user may vary general parameters (e.g. the discount rate and the cost effectiveness threshold for a DALY[1]), and parameters that define vaccine efficacy and the number of required doses. The user may change the set of countries covered by the program manually, by disease burden, and/or using a GNP per capita cutoff. The user can also vary the conditions of adoption, including steady-state adoption rates and the length of time to reach the steady-state.

This Technical Guide explains the calculations in detail in the order that the worksheets appear in the Microsoft Excel file. Since parameters can be modified and results displayed in the graphical user interface (GUI), the user will rarely, if ever, need to refer to these sheets. Users looking to simply use the GUI can refer to the Quick Overview for basic instructions on using the spreadsheet.

A companion document, "A Vaccine Price Guarantee: Estimating Cost and Effectiveness," discusses both the general results of the spreadsheet analysis and sensitivity checks. The book *Strong Medicine: Designing Pharmaceutical Markets to Treat Neglected Diseases* discusses the

[1] DALYs, disability-adjusted life years, are a standard measure of the burden of disease and are defined as the number of healthy years of life lost due to premature death and disability. Refer to Murray and Lopez (1996) for more details.

economic justification for a purchase commitment and guidelines for its design.

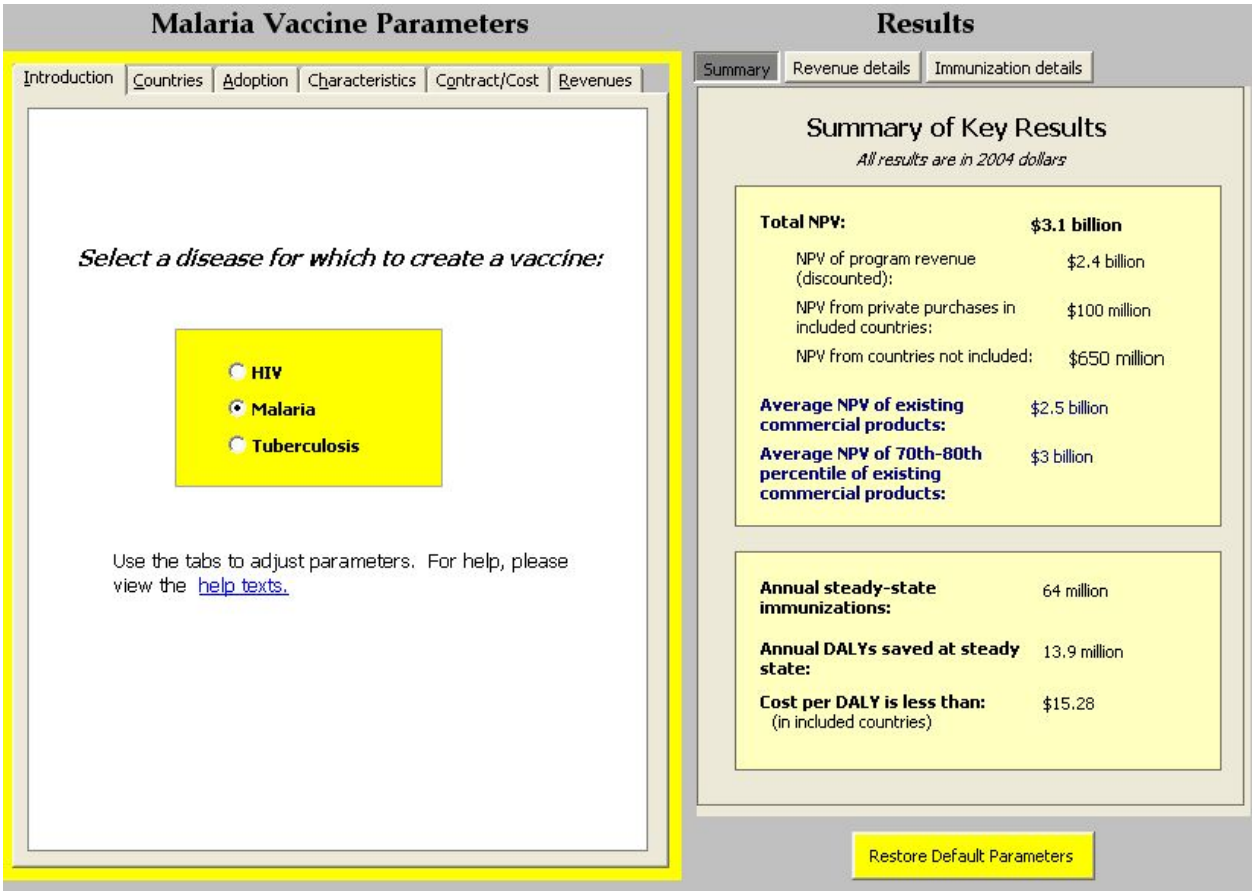
QUICK OVERVIEW

Users who are not interested in a detailed description of how the spreadsheet works but simply in the results of the analysis can change parameters and view results in the graphical user interface (GUI). The GUI opens automatically when the file opens, and can be restarted by clicking the "Launch Vaccine GUI" button on the GUI sheet[2].

The GUI is intended to calculate the cost-effectiveness of a vaccine commitment, and the net present value of revenues that would accrue to a vaccine developer. It can also be used to answer questions such as:

* What contract parameters would provide revenues comparable to existing drugs but also maximize cost-effectiveness?
* What happens if the vaccine requires delivery outside of the Expanded Program of Immunization (EPI) schedule?
* Is a 50% effective malaria vaccine still cost-effective?

[2] In order to use the GUI, Excel must be configured to run macros. To enable macros, go to Tools > Macro > Security, and set the security level to low or medium. Close the spreadsheet and re-open it. If prompted to do so, click "Enable Macros." The GUI should then appaear.



Parameters can be modified on the tabs on the left side of the GUI display, while results are displayed on the panels on the right. The Introduction tab allows the user to select a disease to be analyzed. Input parameters are categorized into **Countries** (countries covered by the program), **Adoption** (levels and rate of vaccine adoption), **Characteristics** (vaccine characteristics, such as efficacy), **Contract/Cost** (price offered, number of people covered, delivery costs, etc), and **Revenues** (revenues from sources outside of the vaccine commitment, such as military and travelers' markets). Explanations of input parameters and default values can be accessed on the **Introduction** tab by clicking on the link to help texts. Each time parameters are modified, the user must hit the return key or click anywhere on the GUI in order to update the results.

The most important results of the analysis (net present value of the revenues to a vaccine developer, annual number of vaccinations in the steady state, DALYs saved, and total cost per DALY saved) are displayed on the **Summary of Key Results** panel. More results can be viewed by clicking on the **Vaccination details** and **Revenue details** buttons.

Further detail on the underlying calculations appears in the following pages, which discuss the worksheets in the order they appear in the spreadsheet.

2. BASIC DATA

This worksheet contains much of the basic data upon which the vaccine calculations are based. For the purpose of the calculations, the population, annual births, GNP per capita, and life expectancy of each country are assumed to be constant over time. Further refinement of the spreadsheet analysis can include variation in these numbers over time.

2.1 COUNTRIES AND CODES

The countries included in the analysis are World Health Organization member states, which are virtually all countries in the world (WHO 1999, WHO 2000). They are the following: Afghanistan, Albania, Algeria, Angola, Armenia, Azerbaijan, Bangladesh, Belarus, Belize, Benin, Bhutan, Bolivia, Bosnia & Herzegovina, Bulgaria, Burkina Faso, Burundi, Central African Republic, Cambodia, Cameroon, Cape Verde, Chad, China, Colombia, Comoros, Congo, Congo DR, Costa Rica, Cote d'Ivoire, Cuba, Djibouti, Dominica, Dominican Republic, Ecuador, Egypt, El Salvador, Equatorial Guinea, Eritrea, Ethiopia, Fiji, Gambia, Georgia, Ghana, Guatemala, Guinea, Guinea-Bissau, Guyana, Haiti, Honduras, India, Indonesia, Iran, Iraq, Jamaica, Jordan, Kazakhstan, Kenya, Kiribati, Kyrgyzstan, Lao, Latvia, Lesotho, Liberia, Lithuania, Macedonia, Madagascar, Malawi, Maldives, Mali, Mauritania, Micronesia, Mongolia, Morocco, Mozambique, Myanmar, Namibia, Nepal, Nicaragua, Niger, Nigeria, North Korea, Pakistan, Panama, Papua New Guinea, Paraguay, Peru, Philippines, Republic of Moldova, Romania, Russian Federation, Rwanda, Samoa, Sao Tome & Principe, Senegal, Sierra Leone, Solomon Islands, Somalia, Sri Lanka, St. Vincent & Grenadines, Sudan, Suriname, Swaziland, Syrian Arab Republic, Tajikistan, Tanzania, Thailand, Togo, Tonga, Tunisia, Turkmenistan, Uganda, Ukraine, Uzbekistan, Vanuatu, Vietnam, Yemen, Yugoslavia, Zambia, Zimbabwe,

Antigua and Barbuda, Argentina, Bahrain, Barbados, Botswana, Brazil, Chile, Croatia, Czech Republic, Estonia, Gabon, Grenada, Hungary, Lebanon, Libya, Malaysia, Malta, Mauritius, Mexico, Oman, Palau, Poland, Saudi Arabia, Seychelles, Slovakia, South Africa, St. Kitts and Nevis, St. Lucia, Trinidad and Tobago, Turkey, Uruguay, Venezuela, Andorra, Australia, Austria, Bahamas, Belgium, Brunei Darussalam, Canada, Cyprus, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Japan, Kuwait, Luxembourg, Monaco, Netherlands, New Zealand, Norway, Portugal, Qatar, Republic of Korea (South Korea), Singapore, Slovenia, Spain, Sweden, Switzerland, United Arab Emirates, United Kingdom, and USA.

The color scheme corresponds with the World Health Organization's regional categories, where:

African Region = AFR = brown
Americas Region = AMR = light blue
Eastern Mediterranean Region = EMR = dark blue
European Region = EUR = orange
South-East Asia Region = SEAR = yellow
Western Pacific Region = WPR = purple

Please see the Appendix A to this document for the World Health Organization List of Member States by Region and Mortality Stratum (WHO 2000, pages 204-5).

Murray and Lopez region codes. Murray and Lopez (1996a) provide data on regional DALY burden by sex and age group. This data is used later in the hiv-aids new cohorts, malaria new cohorts, and tb new cohorts worksheets. Their regional categories are:

chn: China
eme: Established Market Economies
fse: Formerly Socialist Economies of Europe
ind: India
lac: Latin America and the Caribbean

mec: Middle Eastern Crescent
oai: Other Asia and Islands
ssa: Sub-saharan Africa

Please see Appendix B for a list of the countries included in Murray and Lopez regions.

World Bank Code. The World Bank makes the following income classifications (World Bank 2002):

1 = low-income: GNI per capita is $735 or less
2 = lower-middle income: GNI per capita is $736 to $2935
3 = upper-middle income: GNI per capita is $2936 to 9075
4 = high income: GNI per capita is $9076 or more

World Health Organization (WHO) region and sub-region codes. WHO (2000) provides regional DALY burden numbers for HIV, malaria, and tuberculosis. Their publication World Health Report 2000 establishes categories and sub-categories based on region and mortality stratum in the following way. For further information, please see this reference, pages 204 and

AFR1 high child, high adult
AFR2 high child, very high adult
AMR1 very low child, very low adult
AMR2 low child, low adult
AMR3 high child, high adult
EMR1 low child, low adult
EMR2 high child, high adult
EUR1 very low child, very low adult
EUR2 low child, low adult
EUR3 low child, high adult
SEAR1 low child, low adult
SEAR2 high child, high adult
WPR1 very low child, very low adult
WPR2 low child, low adult

2.2 GENERAL COUNTRY DATA

Births 2010-2015. This is the annual number of births predicted for 2010-2015 from the World Health Organization.

Population. This is an indicator for 2000 that comes from the World Bank's World Development Indicators 2002.

GNI per capita. This is 2002 GNI per capita in US current dollars, calculated using the World Bank Atlas method. Please refer to the World Bank per capita income classification described above.

Life expectancy. This is a 2000 figure from World Development Indicators 2002.

2.3 ADJUSTMENT OF DALY FOR COUNTRIES

Ratio of DALY burden averted by preventing disease to DALY burden of disease. The WHO provides information on the DALY burden of disease, which is calculated under the assumption that people would face a very favorable (Japanese female) life expectancy in the absence of the disease. The DALY burden will, in general, be greater than the number of DALYs saved by eliminating the diseases, because the diseases affect countries where people face many other competing risks. DALYs saved in countries with relatively low life expectancies would be overestimated without the ratio of DALY burden adjustment. The ratio equals the present value of one dollar each year of the life expectancy of a country at the real interest rate divided by the

present value of one dollar each year for 81.25 years (the life expectancy of a Japanese woman) at the real interest rate.

2.4 COUNTRY ELIGIBILITY

IDA eligibility/coding. If a country is eligible for World Bank International Development Association (IDA) loans, then the cell equals one, and zero otherwise. IDA eligibility is based on (1) relative poverty, (2) weak creditworthiness, and (3) good economic and social policy performance. Refer to http://www.worldbank.org/ida/ for more information. Although this variable does not enter into any of the calculations, it is provided here for the user's reference.

Commitment eligibility. If a country is eligible to participate in at least one vaccine fund purchase program, then the cell equals one; if the country is ineligible to participate, then the cell equals zero. Eligibility is determined by comparing the countries GNP per capita with a cutoff point, which can be adjusted by the user on the options worksheet.

3. AGE DISTRIBUTION

This worksheet contains the age distribution for each country in five-year intervals for the year 2000.

The interpretation of this data is straightforward. For example, about 8% of China's population is under the age of 5, and about 10% are between the ages of 30 and 35. This is calculated from World Population Projections, International Bank for Reconstruction and Development / World Bank Group, 2000, which is reported in World Development Indicators 2000. For the purpose of the calculations, the age distribution in each country is assumed to be constant over time. Further refinement of the spreadsheet analysis can include change in the population distribution in a country over time.

4. FERTILITY

This worksheet displays the distribution of births to women ages 15-50 in each country for the year 2000.

The interpretation of this data is straightforward. For example, about 36% of China's births were to women between the ages of 25 and 29, and about 15% of births were to women between the ages of 35 and 39. These are 2000 figures calculated from U.S. Bureau of the Census, International Data Base, Table 028: "Age-Specific Fertility Rates and Selected Derived Measures." The data can be found on the internet at http://www.census.gov/ipc/www/idbnew.html

For the purpose of the calculations, the fertility distribution in each country is assumed to be constant over time. Further refinement of the spreadsheet analysis in the future can include change in the fertility distribution in a country over time.

5. HIV-AIDS CASES

This worksheet estimates the distribution of HIV-AIDS burden among countries within the same WHO region.

5.1 ESTIMATING DISTRIBUTION OF DISEASE BURDEN

WHO does not report country-level data for burden of disease, but only regional data. To calculate cost effectiveness of a country-based vaccine purchase commitment, however, it is necessary to calculate country-level burdens. Therefore, regional burden is divided according to the distribution of burden among countries within each region based on USAIDS data of HIV seroprevalence. The data comes from the Epidemiological Fact Sheets by Country (June 2000), which report the estimated number of HIV positive 0 to 49 year olds at the end of 1999. See http://www.unaids.org/hivaidsinfo/statistics/june00/fact_sheets/

UNAIDS data on HIV seroprevalence in a country are in column E. First, the number of HIV-positive people for all countries in a particular region are aggregated. The fourteen regional totals appear at the bottom of the worksheet. Then the country number is divided by the regional total to obtain the country's proportion of seroprevalence in its region. As the DALY burden is not perfectly correlated with the rate of HIV seroprevalence, there will be a degree of error in using these shares to distribute the WHO regional burden data among countries within a particular region.

5.2 ADJUSTING FOR MISSING VALUES

The following countries have no data on HIV seroprevalence and are indicated by an asterisk in column F: Andorra, Antigua and Barbuda, Cape Verde, Dominica, Grenada, Kiribati, Micronesia, Monaco, Palau, Samoa, Sao Tome and Principe, Seychelles, Solomon Islands, St. Kitts and Nevis, St. Lucia, St. Vincent and Grenadines, Tonga, Vanuatu, Somalia.

To fill in these values in column E, the average percent of population that is HIV positive for the country's WHO subregion is multiplied by the country's population. Adjusting for missing data in this way has no important impact on the results, as these countries have only a small fraction of the worldwide HIV/AIDS burden.

6. MALARIA CASES

This worksheet estimates the distribution of malaria burden among countries within the same WHO region.

6.1 ESTIMATING DISTRIBUTION OF DISEASE BURDEN

Since country-by-country figures on malaria burden are unavailable, a proxy for burden is used to estimate the distribution of DALYs within regions. For this purpose, numbers on high and low probability of getting malaria in a country are used. This data comes from the WHO's "World Malaria Situation in 1994, Part I" (WHO 1997c).

Column G. To obtain the malaria "burden" in a country, the country's 2010-2015 population is multiplied by a linear combination of low and high probabilities. A parameter in the options worksheet allows the user to change the linear combination of low and high probabilities as desired. For example, if 20 percent of the people in a country (with population 1000) live in low-risk areas, 50 percent live in high-risk areas, and 30 percent live in areas without malaria, the estimated "burden" for the country is (1 x 0.2 x 1000) + (10 x 0.5 x 1000). Of course, the malaria cases parameter can change the weighting of the high and low risk variables, as the user desires. Please note that the distribution of burden that is ultimately obtained (column I) is not very sensitive to the particular value for this parameter.

Column H. The country "burden" numbers are aggregated according to the fourteen WHO categories.

Column I. The country “burden” is divided by the total regional “burden” to get that country’s share of malaria burden of its region.

7. TB CASES

This worksheet estimates the distribution of tuberculosis burden among countries within the same WHO region.

7.1 ESTIMATING DISTRIBUTION OF DISEASE BURDEN

WHO does not report country-level data for burden of disease, but only regional data. It is, nevertheless necessary to have country-level estimates. Therefore, regional burden is divided according to the distribution of burden within the region.

The data on the estimated incidence of tuberculosis in 1998 is listed in column D. The data come from WHO's Global Tuberculosis Control 2000 (WHO 2000b). Please see: http://www.who.int/gtb/publications/globrep00/download.html

Then the number of cases for each WHO region are aggregated (column E). Finally in column F, the country cases are divided by the region cases to get a country's proportion of cases in its region. This is used as the estimate for the distribution of tuberculosis burden (in DALYs) within regions.

8. DISEASE TYPES

This worksheet describes which disease types are prevalent in each country given the vaccine is effective against those types.

It is possible that a vaccine developed for HIV/AIDS (or malaria) will not be effective against all HIV-1 subtypes (or malaria species). As these subtypes follow a distinct geographical distribution, this vaccine characteristic may have an extremely significant effect on the number of DALYs saved. Therefore, the options worksheet lets the user specify which malaria species and HIV-1 subtypes the vaccine will be effective against. To operationalize this set of parameters, the spreadsheet includes information on which disease types are prevalent in each country.

8.1 HIV/AIDS SUBTYPES

Columns G through O show HIV-1 subtypes by country. A value of 1 means that the HIV subtype is prevalent in the country AND the HIV/AIDS vaccine is effective against the subtype (see options for this set of parameters). A value of 0 means otherwise (EITHER the vaccine is effective against the subtype, but the subtype is not prevalent in the country; OR the subtype is prevalent, but the HIV vaccine does not work against it).

Column P shows which countries have any prevalent subtype against which the HIV vaccine is effective. Warning: If two subtypes are prevalent in a country and the vaccine is only effective against one of the subtypes, the spreadsheet currently assumes the vaccine will still be able to avert the same amount of burden as if the vaccine were effective against both subtypes in the

country. Therefore, this analysis will produce an overoptimistic picture of the effects of vaccines effective against only some subtypes. Further work will refine the treatment of multiple subtypes prevalent in a particular country.

The geographic distribution of HIV is:

A Central and East Africa
B Americas/ Europe/ Japan/ Australia/ Asia
C Sub-Saharan Africa/ India/ Brazil
D Central and East Africa
E C. African Rep/ Thailand
F Brazil/ Romania
G Russia/ Gabon
H Zaire/ Cameroon
O Cameroon/ Gabon

For more information please refer to http://www.unaids.org and Osmanov, Heyward, and Esparza (1996).

8.2 MALARIA SPECIES

Columns W through Y show malaria species by country. A value of 1 means that that malaria species is prevalent in the country AND the malaria vaccine is effective against the species (see options for this parameter). A value of 0 means otherwise (EITHER the vaccine is effective against the species, but the species is not prevalent in the country; OR the species is prevalent, but the malaria vaccine does not work against it).

Column Z shows which countries have any prevalent species against which the malaria vaccine is effective. Warning: If two malaria species are prevalent in a country and the vaccine is only effective against one of the species, the spreadsheet currently assumes the vaccine will still be

able to avert the same amount of burden as if the vaccine were effective against both species in the country. Therefore, this analysis will produce an overoptimistic picture of the effects of vaccines effective against only some species. Further work will refine the treatment of multiple species prevalent in a particular country.

As listed in the options documentation, the geographic distribution of malaria is:

> Plasmodium falciparum Africa, Haiti, Dominican Rep, EMR2, SEAR1, SEAR2, WPR2
> Plasmodium vivax Asia, Middle East, Oceania, Americas, Europe
> Plasmodium malariae Cambodia, Myanmar, Laos, Thailand

For more information please refer to http://www.malaria.org and http://mosquito.who.int/

9. OPTIONS

This worksheet describes the parameters in the model that the user may vary. The GUI takes inputs from the user and modifies the cells in this sheet. In the spreadsheet there are a few numbers that are highlighted in color. These are automatically set and should not be changed.

ASSUMPTIONS OF THE MODEL

9.1 GENERAL PARAMETERS

Inflation rate. The default inflation rate is assumed to be 3%.

Real discount rate. The real discount rate is used to discount future costs and benefits, such as lives saved, which are presented in real terms. The default real discount rate is 3%, which is selected for comparability with other cost effectiveness studies in health. Note that if the discount rate is increased for comparability with non-health investments, the implicit DALY cost effectiveness threshold should be raised as well, since the cost effectiveness threshold is based in large part on looking at other potential health investments.

Nominal discount rate. The nominal discount rate is used to discount future nominal cash payments. As inflation is assumed to be 3% and the real discount rate is assumed to by 3%, the default nominal rate is 6%. To change the nominal discount rate, the user should adjust the real discount rate and/or the inflation rate.

Dollars per DALY Cost-effectiveness Threshold. The user has the option to limit vaccine administration to those countries where a mass vaccination program would be cost effective at

delivery cost (not including cost of manufacture or development). This number determines the cutoff for what is considered cost effective in terms of dollars per DALY saved. The base case is $100/per DALY. In the 1993 World Development Report, the World Bank refers to several health interventions in developing countries, which cost in the range of $25 to $150 per DALY. In these instances, it is implied that these interventions are considered "highly cost effective" (World Bank 1993, pages 8, 64, and 68). Health interventions are considered cost-effective in the U.S. at $50,000-$100,000 per year of life saved (Neumann et al., 2000). The implied ratio of U.S. to developing country DALY thresholds far exceeds the corresponding ratio of GDP. Thus, the DALY threshold may be considered conservative.

GNP per capita program eligibility cutoff. If a country has per capita GNP lower than this number, then the country may participate in the vaccine purchase commitment; the country is considered "covered." Note that not all countries that are eligible for program participation may receive vaccinations, as vaccination in an eligible country must be cost effective for that country to participate in the program. The default value is $1,000 GNP per capita, which is the cutoff for Vaccine Fund eligibility.

9.2 BASIC VACCINE COVERAGE

The spreadsheet draws a distinction between "new cohorts", "children" and "old cohorts." The definitions of these groups are disease dependent and reflect some subjective assumptions about the best way to distribute vaccines given the distribution of DALY burden over age groups.

For the case of tuberculosis, “new cohorts” includes newborns, “children” includes children aged 1-10 at the time the vaccine is developed, and “old cohorts” includes people 11 or more years old at the time the vaccine is developed. The calculation assumes that new cohorts are vaccinated each year, while some fraction of children and old cohorts are vaccinated over the initial years of the program.

For malaria, the “new cohorts” category is comprised of newborns. “Children” reflects the population of 1-5 year olds existing at the time the vaccine is developed, who have not yet gained natural immunity to the disease. “Old cohorts” are comprised of women pregnant with their first child, who temporarily lose their natural immunity. The calculation assumes that newborns and women who become pregnant with their first child will be vaccinated every year, while the stock of children aged 1-5 years at the time the vaccine is developed will be immunized over the initial years of the program.

The HIV/AIDS case differs substantially from the others in that the risk of contracting the disease as a child is relatively low. Thus especially for vaccines whose efficacy wears off after a limited number of years, it may be more cost-effective to immunize children each year rather than newborns. “New cohorts” are thus defined to be ten-year olds, and “old cohorts” consist of all people 11 years or older at the time the vaccine is developed.

% of new cohorts vaccinated. The percent of new cohorts that will receive a particular vaccination if three doses are required (user-entered uniform rate). The default coverage rate is the 2002 DPT3 (diphtheria, pertussis and tetanus) vaccination rate plus five percentage points, as

displayed on the "coverage" worksheet[3]. However, the user can also choose to specify a single rate for all countries, which would be displayed in this cell. This coverage rate encompasses decisions of individuals whether to participate given that their country is covered by the program.

% of children vaccinated. The percent of children that will receive the vaccination. The default coverage rate for children is 10%. This coverage rate encompasses decisions of individuals whether to participate given that their country is covered by the program.

% of old cohorts vaccinated. The percent of old cohorts that will receive the vaccination. The default coverage rate is 30% for hiv and tuberculosis.. The default coverage rate for malaria is based on immunization rates for the tetanus toxoid (TT2) vaccine, which is targeted towards pregnant women. The default rate is the 2002 TT2 rate plus five percentage points.

9.3 COVERAGE WHEN MORE THAN ONE DOSE IS NECESSARY

It is likely that vaccine coverage will be further reduced if extra doses are necessary. The following set of parameters affects vaccine coverage for the three cohorts when a vaccine requires several doses to remain effective. **NOTE: Since the current set of defaults set the coverage rates to levels for a three-dose vaccine rather than a one-dose vaccine, this function has been disabled, but left in place in case it may become appropriate to use this in later versions of the spreadsheet.**

[3] Immunzation data obtained from the WHO are available online at http://www3.who.int/whosis/menu.cfm?path=whosis,topics,immunization&language=english

% of new cohorts/ children/ old cohorts who receive each additional dose. The percent of new cohorts, children, and old cohorts, respectively, that receives each additional dose. The base case assumption is 100%, as the default coverage rate is for a three-dose vaccine.

9.4 PARAMETERS RELATED TO COSTS

9.4.1 STANDARD DELIVERY COSTS

EPI delivery cost. The cost of adding a vaccine to the EPI package defaults to $0.75. The base case is that of a vaccine which could be added to the standard package of vaccines that are delivered under the Expanded Program on Immunization (EPI) package. This package currently makes three contacts with each child costing about $15.00. (World Bank 1993b, page 168). This is roughly $5.00 per contact. The addition of both the hepatitis B and the yellow fever vaccines (which are relatively expensive) to the EPI increased the $15 cost of the program by 15%, or $2.25, including both manufacturing and distribution costs.

 # Doses above EPI. The number of doses which cannot be delivered with the EPI schedule For instance, vaccine may be contraindicated with existing EPI vaccines, require delivery at different ages for newborns, or require more than three doses.

Per-dose cost of extra doses. The cost of delivering each dose incompatible with the EPI schedule.

Total delivery cost: The sum of the cost of adding to the EPI schedule and the cost of doses outside the EPI schedule.

9.4.2 MARGINAL MANUFACTURING COSTS

Marginal manufacturing cost of one additional dose given a very high manufacturing volume. This variable does not include R&D costs for the vaccine or costs for developing bulk manufacturing systems. It is the cost of producing enough additional vaccine to immunize one additional person, given that large-scale production is already taking place. The package of five vaccines in the EPI program sells for $0.50 and vaccines would be purchased in bulk under the program (Robbins and Freeman, 1988). **NOTE: This function is currently not integrated into the spreadsheet. These cells should be non-zero only if the user wants to use the delivery cost plus manufacturing cost in the calculations of cost-effectiveness to determine whether countries should be covered by the vaccine commitment (on the malaria cost worksheet).**

9.5 OTHER PARAMETERS

Malaria cases parameter. On the malaria cases worksheet, the formula in column H involves a linear combination of the "low probability of getting malaria" and "high probability of getting malaria" to obtain a measure of malaria burden in each country. The overall purpose of this worksheet is to estimate the distribution of malaria burden among countries within regions. In order to increase the flexibility of this formula, which combines low and high probabilities to yield a proxy for country burden, the malaria cases parameter allows the user to adjust the relative weights in the algorithm. In more formal terms, let country population equal P, the proportion of the population in low malaria burden areas equal A, the proportion of the population in high malaria burden areas equal Z, and the malaria cases parameter equal M. Therefore, the formula in column H equals P*(1*A + M*Z).

Targeting factor for old cohorts. Vaccination programs can be targeted to high-risk groups using criteria other than age and nation of residence. For example, a potential malaria vaccine can be targeted to geographic areas with a particularly high burden of malaria. A tuberculosis vaccine can be targeted to people in prisons and urban slums with high prevalence of the disease. An HIV/AIDS vaccine can be targeted to soldiers and sex workers. It is assumed that there is no effective targeting for new cohorts or children, but that the vaccination of older cohorts is targeted to high-risk people. For example, only women pregnant with their first child receive the malaria vaccine. Murray and Lopez (1996) estimate the burden of malaria for 15-44 year old females is about 25% higher than that for 15-44 year old males. If this is due entirely to the greater burden on first-time mothers, and if 1/20th of these women are first-time mothers, then this implies their malaria burden is about five times higher than the average burden for a 15-44 year old person. Therefore, the default value for targeting first-time pregnant women is five. The user may set the targeting factor to one to simulate no gains to targeting.

PARAMETERS RELATED TO VACCINE CHARACTERISTICS

The default values for the parameters in this section correspond to the base case. The user can vary these values to create a less-than-ideal vaccine.

9.6 EFFECTIVENESS OF THE VACCINE

Vaccine efficacy. The percentage of vaccinated people who are effectively protected against the disease.

Number of years the vaccine is effective. This controls the number of years a vaccine remains effective. Denote the number of years the vaccine is effective as T. This implies, for a particular individual, a vaccine remains effective from the age at which the person receives the vaccination, say age Y, to the age Y+T. The maximum allowable value is 20 years. Warning: the spreadsheet does not yet take into account the fact that a person may receive a second vaccination after the first vaccination becomes ineffective. Therefore, the user is cautioned that the spreadsheet currently severely underestimates the cost effectiveness of vaccines that are only effective for a limited number of years. Further work will rectify this problem, but one way to simulate a vaccine that protected for only a year would be to enter it as a 5-dose vaccine that required 3 doses outside of the EPI schedule and lasted for 5 years.

Scaling factor for benefits ages 0-4. This factor scales down the DALYs saved from protection from the disease in the 0-4 age group. This may be necessary if the vaccine cannot be given to infected people as infants or if the vaccine is not as effective for infants. For example, an HIV vaccine might not prevent transmission from mother to infant or might only protect against transmission through breast milk, but not against transmission during birth. A default value of 100% allows the vaccine to effectively protect the 0-4 age group. A value of 20% would reduce the DALYs saved for the ages 0-4 by 80%.

9.9 CLINICAL USE AND CONTRA-INDICATED CONDITIONS

NOTE: These parameters cannot be altered through the GUI, but may be altered manually in the options sheet if the user wishes.

Clinical use. If one or more of the target cohorts cannot receive the vaccine for medical reasons, then this parameter equals zero. If, in general, the target group may receive the vaccine, then the parameter equals one. For example, pregnant women cannot receive some vaccines. Generally, the administration of live attenuated vaccines should be avoided in pregnancy and inactivated vaccines should not be given until the second trimester. Certain vaccines, like rubella, are contraindicated in women who are pregnant or may become pregnant within three months following administration. In addition, some vaccines may not be given to new cohorts.

Contra-indicated condition. A certain portion of the population may have allergies that would cause them to have anaphylactic shock if they received the vaccine. For example, an influenza vaccine cannot be given to people with allergies to eggs (Riddiough et al. 1983). Thus, this parameter specifies the percent of a target group that cannot receive the vaccine on account of a certain prevalence of a contra-indicated condition or disease. If there were, in fact, a contraindicated condition, then it would be necessary to take into account the additional costs of screening for this condition in potential vaccine recipients. Thus, a contra-indicated condition may affect the overall cost-effectiveness of the purchase program. Another parameter described below, additional clinical costs, allows the user to introduce possible testing costs into the calculations.

9.10 OTHER CLINICAL COSTS

Additional clinical costs. This parameter allows the user to account for any other clinical costs over and above those the base case considers. In order to add costs, simply set the dichotomous

parameter to one and specify the desired percent of "extra costs." Testing for contra-indicated conditions prior to the administration of a vaccine is an example of additional clinical costs that may affect the cost effectiveness of the purchase program. **NOTE: This option is not functional in the current spreadsheet.**

9.11 VACCINE EFFICACY AGAINST DISEASE TYPES

HIV-1 Subtypes. Not every possible HIV vaccine may be effective against all subtypes of HIV. With this set of parameters, the user may specify against which subtypes (A, B, C, D, E, F, G, H, and O) the vaccine will be effective. A value of one indicates that the vaccine is effective against the particular subtype; a zero indicates the vaccine will not be effective against the subtype. Warning: If two subtypes are prevalent in a country and the vaccine is only effective against one of the subtypes, the spreadsheet currently assumes the vaccine will still be able to avert the same amount of burden as if the vaccine were effective against both subtypes in the country. Therefore, this analysis will produce an overoptimistic picture of the effects of vaccines effective against only some subtypes. Further work will refine the treatment of multiple subtypes prevalent in a particular country.

The geographic distribution of HIV subtypes is listed here but refer to the documentation for the disease types worksheet for more information.

Subtype Regions
A Central and East Africa
B Americas/ Europe/ Japan/ Australia/ Asia
C Sub-Saharan Africa/ India/ Brazil
D Central and East Africa
E C. African Rep/ Thailand
F Brazil/ Romania
G Russia/ Gabon

H Zaire/ Cameroon
O Cameroon/ Gabon

Malaria Species. Analogously, not every malaria vaccine may be effective against all species of malaria. Here the user may specify which species (Plasmodium falciparum, P. vivax, P. malariae) the vaccine will be effective against. 1 indicates that the vaccine is effective against the particular species; 0 indicates the vaccine will not be effective against the species. Warning: If two malaria species are prevalent in a country and the vaccine is only effective against one of the species, the spreadsheet currently assumes the vaccine will still be able to avert the same amount of burden as if the vaccine were effective against both species in the country. Therefore, this analysis will produce an overoptimistic picture of the effects of vaccines effective against only some species. Further work will refine the treatment of multiple species prevalent in a particular country.

9.12 ADDITIONAL PARAMETERS

# of People Vaccinated at High Price. This parameter sets the number of people vaccinated at the initial high price under the program.

Nominal Cost of Capital (High Risk). Revenues to the vaccine developer are uncertain, so they should be discounted at a high-risk rate which can be approximated as the average return on the stock market. The default value of this parameter is 11 percent.

Real Cost of Capital (High Risk). The cost of capital in real terms rather than nominal terms (adjusted for inflation). The default value of this parameter is 8 percent.

Initial (high) Price Per Person, User-Defined 2004. The real initial high price paid by the program sponsor in 2004 dollars. The contract should stipulate that the nominal price be inflation-adjusted, so that the real value of the revenues to a vaccine developer does not drop for vaccines that would take longer to develop. The default high price is $15. If it took 10 years for a vaccine to be developed, the inflation-adjusted price in nominal terms would be about $20.

Low Price Per Person, user-defined 2004. The price of the vaccine after program purchases end in 2004 dollars. As with the high price, the nominal low price should be adjusted for inflation so that the real value of the revenues remains constant over time. The default low price is $1.

% vaccinated on top of DPT3. The GUI gives the user the option to define takeup rates as the country-by-country DPT3 takeup rates plus (or minus) this fixed number of percentage points. The DPT3 rates serve as a useful proxy of the condition of a country's health infrastructure, but adoption rates for a malaria vaccine may differ from DPT3 rates if, for instance, parents value a vaccine against malaria more highly than the DPT3 vaccines. Thus the default value is 5 percent.

Flag if Default to DPT3 Takeup Rates. This flag is set to 1 if the user chooses to base vaccine adoption rates on the DPT3 data, and 0 if not.

DPT1, DPT3, measles: The user can base rates on several benchmark immunization rates – those for the first dose of the diphtheria/pertussis/tetanus vaccine (DPT1), those for the third dose of the diphtheria/pertussis/tetanus vaccine (DPT3), or those for the measles vaccine.

Years until Vaccine Developed. Number of years in the future that the vaccine is developed (e.g. if a vaccine is developed in 2014, this is set to 10). Currently this parameter is set to 10 years, and cannot be modified by the user.

Years from Development to Steady State. This parameter allows the user to vary the speed with which people adopt the vaccine. The final "steady-state" vaccination rates can be specified by the user as country-by-country rates based on the DPT3 vaccine takeup rates, or entered separately. Presumably, people will not immediately get vaccinated at those rates, but slowly adopt the technology over time. This parameter specifies the number of years it takes for adoption rates to increase up to the steady-state rates specified by the user, assuming that takeup rates increase linearly over time.

High Price, Time of Development. This is the nominal high price that would be paid at the time the vaccine was developed, adjusted for inflation. In real terms, this is equivalent to the high price entered by the user in 2004 dollars.

Low Price, Time of Development. This is the nominal low price that would be paid at the time the vaccine was developed, adjusted for inflation. In real terms, this is equivalent to the low price entered by the user in 2004 dollars.

Year of Development. This is simply 2004 + (number of years until vaccine is developed).

Additional Revenues from Non-Covered Countries. The vaccine developer will also gain revenues from non-program sales in middle-income countries, and sales to travelers and the military.

Average NPV of 70th to 80th Percentile of Existing Products (2004 $). Perhaps the most attractive approach is to look at concrete evidence on the revenue needed to induce research on pharmaceuticals in high-income countries.

The most recent comprehensive analysis of sales revenue for pharmaceutical products is by Grabowski et al. (2002), in which the authors report on 118 NCEs introduced into the United States between 1990 and 1994. Using an estimated industry-wide nominal cost of capital of 11 percent, the net present value (at the time of market introduction) of sales of the average product in their sample was $2.8 billion in year 2004 dollars.

In thinking about the necessary value of a vaccine commitment, one may need to adjust these figures since the revenues reported by Grabowski et al. (2002) were partially spent on marketing. And under a vaccine commitment program, a potential vaccine manufacturer would need to spend considerably less on promotion. Rosenthal et al. (2002) estimate that, relative to sales, expenditures on promotion by U.S. pharmaceutical companies has remained fairly constant at

about 15 percent of revenue, and has fallen slightly since 1998. Promotion/sales ratios are believed to be lower in Europe and elsewhere.

Making a ten percent adjustment for lower marketing costs, $2.5 billion in 2004 dollars in net present value of sales would be needed to match the average revenue brought in by NCEs. Of course the sample of existing products includes the "low-hanging" fruit of products that were easy to develop. To the extent that developing a malaria vaccine is more technologically challenging than developing the typical product, the appropriate payment would be greater. To get a sense of how much more than the average might be appropriate to pay we look at revenues from the more lucrative tail of the distribution. Again, using figures from Grabowski et al, products between the 70th and 80th percentile of the distribution earned an average of $3.4 billion (2004 dollars) in net present value of revenues, while.those between the 80th and 90th percentile earned $5.5 billion in 2004 dollars. Adjusted for marketing costs, products between the 70th and 80th percentile brought in an average of $3.0 billion in net present value of revenues and those between the 80th and 90th percentile brought in $5.0 billion (both in 2004 dollars). The average of the 70^{th} to 80^{th} percentile is a useful benchmark because it represents a substantial improvement over the mean revenue but does not attempt to match the top blockbuster drugs..

Flag if Pregnant Women Takeup Based on TT2. Set to 1 if the user chooses to base immunization rates for pregnant women on tetanus toxoid immunization rates. These rates serve as a useful proxy of the condition of a country's health infrastructure, and particularly for the amount of healthcare available to pregnant women.

% Immunized on Top of TT2. The GUI gives the user the option to define takeup rates as the country-by-country TT2 takeup rates plus (or minus) this fixed number of percentage points.

Average NPV of existing products (2004 $). The average of all products in the data analyzed by Grabowski et al (2002).

Years that Commitment Advances Development. This option is only available in the version of the spreadsheet for special applications, and does not appear in the basic Vaccine Speradsheet. In the absence of a price commitment both development and adoption of the vaccine could be delayed. It is difficult to know how much a vaccine commitment would speed vaccine development, but one indication that the effect is likely to be substantial comes from the Orphan Drug Act. While only ten new orphan drugs were discovered in the decade prior to the Orphan Drug Act, 200 were discovered in the next decade. The default value is 10 years.

Years that Commitment Advances Adoption. This option is only available in the version of the spreadsheet for special applications, and does not appear in the basic Vaccine Speradsheet. A vaccine commitment is also likely to substantially accelerate access in the poorest countries. As noted earlier, when the hepatitis B vaccine was introduced at $30 per dose, it was rarely used in low-income countries (Muraskin 1995; Galambos 1995). Even at a dollar or two per dose, hepatitis B and Haemophilus influenzae b vaccines still do not reach most children in the poorest countries (General Accounting Office 1999). The historical record suggests adoption of new vaccines in developing countries could easily be delayed by ten to fifteen years in the absence of a commitment. The default value is 10 years.

Total Years Advanced by Commitment. This option is only available in the version of the spreadsheet for special applications, and does not appear in the basic Vaccine Speradsheet. The number of years that the commitment advances development added to the number of years the commitment advances adoption.

Lag Between Infection and Onset of Disease. Especially in the case of HIV, there may be a significant lag between infection and the onset of disease. For example, if this lag were ten years, then immunizing ten-year-olds would avert the DALY burden observed for 20-30 year-olds.

10. VACCINATIONS

This worksheet displays the number of vaccinations for each disease (covered, non-covered countries, and all countries).

10.1 NEW COHORT VACCINATIONS

Row 4. This lists the sum of the number of annual births in all covered countries and the number of first-time mothers in the case of malaria. These numbers come from the hiv-aids, malaria, and tb worksheets.

Row 5. This displays the number of new cohorts actually vaccinated each year from the hiv-aids coverage, malaria coverage, and tb coverage worksheets.

10.2 CHILDREN VACCINATIONS

Row 7. This lists the number of children ages one to five (one to ten for hiv-aids and tb) in all covered countries. These numbers come from the hiv-aids, malaria, and tb worksheets.

Row 8. This displays the number of children actually vaccinated from the hiv-aids coverage, malaria coverage, and tb coverage worksheets. Note that these "backlogged" vaccinations are distributed the transition years of the program.

10.3 OLD COHORT VACCINATIONS

Row 10. This lists the number of people ages 10 to 35 (for HIV/AIDS and TB). These numbers come from the hiv-aids and tb worksheets.

Row 11. This displays the number of people ages 10 to 35 vaccinated from the hiv-aids coverage and tb coverage worksheets.

10.4 TOTAL NUMBER OF PEOPLE VACCINATED IN STEADY STATE

Row 13. This adds up the number of people (in any cohort) receiving vaccinations every year in the steady-state.

10.5 NUMBER OF COUNTRIES THAT RECEIVE VACCINATIONS

Rows 15 through 18. Lists the number of countries getting new cohort, children, old cohort, and any vaccinations, respectively.

Row 20. This row shows the fraction of countries that receive vaccinations that are IDA eligible. Please see the notes on IDA eligibility in the documentation for basic data.

11. HIV-AIDS

This worksheet is an intermediate calculation of the numbers of people vaccinated and DALYs saved, assuming 100% coverage. Note that for HIV/AIDS, the calculation assumes that new cohorts are comprised of ten year olds, old cohorts are comprised of those 11 or older, and vaccinations are not given to children under the age of 10. The cells labeled “children” do not affect the calculations and are kept simply to maintain symmetry with the sheets that analyze the malaria and tuberculosis cases.

11.1 NEW COHORTS IN COVERED COUNTRIES

Column B lists the burden of HIV/AIDS in DALYs per ten year old from the hiv-aids children worksheet. This number can be considered the marginal benefit of a successful intervention, given the user-entered duration of protection.

Column C displays the number of births in one year in the country for covered countries which have disease prevalence. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column D finds the co-payments that a country will pay for new cohort vaccinations (unadjusted by the coverage rate). **NOTE: This function is currently inactive.**

Column E gives the number of DALYs that would be saved if all new cohorts in covered countries received the vaccination.

Column F records which countries receive new cohort vaccinations.

11.2 NEW COHORTS IN NON-COVERED COUNTRIES

Columns G through I are analogous to the previous section.

11.3 CHILDREN IN COVERED COUNTRIES

These cells are not used in the calculation.

11.4 CHILDREN IN NON-COVERED COUNTRIES

These cells are not used in the calculation.

11.5 OLD COHORTS IN COVERED COUNTRIES

Column R lists the burden of HIV/AIDS in DALYs per old cohort from the hiv-aids old cohorts worksheet. This number can be considered the marginal benefit of a successful untargeted vaccination, given the duration of protection of the vaccine.

Column S displays the number of 10 to 35 year olds in the country. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column T finds the co-payments that a country will pay for old cohort vaccinations (unadjusted by the coverage rate). This function is currently inactive.

Column U gives the number of DALYs saved for those old cohorts that receive effective vaccinations. This is the DALY burden per old cohort times the number of vaccinations times the vaccine efficacy times the ratio of DALY burden (see notes for the options worksheet).

Column V records which countries receive old cohort vaccinations.

11.6 OLD COHORTS IN NON-COVERED COUNTRIES

Columns W to Y are analogous to the previous section.

11.7 COUNTRIES RECEIVING VACCINATIONS

Columns Z through AD list the covered countries receiving any vaccination, non-covered countries receiving any vaccination, any country receiving any vaccination, IDA eligibility for Commitment participating countries, and IDA eligibility for non-Commitment participating countries, respectively.

12. HIV-AIDS COVERAGE

This worksheet obtains the number of vaccinations and DALYs saved for both covered and non-covered countries at the coverage rate specified in the "coverage" worksheet.

12.1 NEW COHORTS IN COVERED COUNTRIES

Column B lists the DALY burden of HIV/AIDS per ten year old from the hiv-aids children worksheet. This number can be considered the marginal benefit of a successful intervention, given the duration of protection of the vaccine..

Column C displays the number of births in one year in the country for covered countries which have disease prevalence. This number is adjusted for the vaccine coverage rate. For more information on coverage rates, see the documentation for the "coverage" worksheet.

Column D finds the co-payments that a country will pay for new cohort vaccinations (adjusted by the coverage rate). **NOTE: This function is currently inactive.**

Column E gives the number of DALYs that would be saved at the coverage rate, given the efficacy of the vaccine.

Column F records which countries receive new cohort vaccinations.

12.2 NEW COHORTS IN NON-COVERED COUNTRIES

Columns G through I are analogous to the previous section.

12.3 CHILDREN IN COVERED COUNTRIES

These cells are not used in the calculation.

12.4 CHILDREN IN NON-COVERED COUNTRIES

These cells are not used in the calculation.

12.5 OLD COHORTS IN COVERED COUNTRIES

Column R lists the DALY burden of HIV/AIDS in DALYs per old cohort from the hiv-aids old cohorts worksheet. This number can be considered the marginal benefit of a successful untargeted vaccination.

Column S displays the number of 10 to 35 year olds in the country adjusted for the vaccine coverage rate.

Column T finds the co-payments that a country will pay for old cohort vaccinations (adjusted by the coverage rate). This function is currently inactive.

Column U gives the number of DALYs saved for those old cohorts that receive effective vaccinations. This is the DALY burden per old cohort times the number of vaccinations at the coverage rate times the vaccine efficacy times the ratio of DALY burden (see notes for the options worksheet).

Column V records which countries receive old cohort vaccinations.

12.6 OLD COHORTS IN NON-COVERED COUNTRIES

Columns W to Y are analogous to the previous section.

12.7 COUNTRIES RECEIVING VACCINATIONS

Columns Z through AD list the covered countries receiving any vaccination, non-covered countries receiving any vaccination, any country receiving any vaccination, IDA eligibility for Commitment participating countries, and IDA eligibility for non-Commitment participating countries, respectively.

13. HIV-AIDS COST

This worksheet calculates the discounted sum of DALYs saved by the program in each country over a 50 year horizon, the number of vaccinations in each country in each year given the takeup rates, and the discounted sum of the costs of delivery in each country. It then flags countries for which vaccination would not be cost-effective relative to the $100 threshold at delivery cost.

Rows 5 to 189, Columns B to AY calculate the discounted DALYs saved in each year given the takeup path specified by the user. The calculation assumes a linear takeup path to the steady-state level for new cohorts. Vaccinations of children and old cohorts are distributed over the transition to the steady state. Future DALYs are discounted using the real discount rate.

Rows 197 to 381, Columns B to AY calculate the number of vaccinations in each country in each year given the takeup path specified by the user. The calculation assumes a linear takeup path to the steady-state level for new cohorts. Vaccinations of children and old cohorts are distributed over the transition to the steady state.

Rows 387 to 571, Columns B to AY calculate the discounted cost of delivery of vaccinations in each year given the takeup path specified by the user. If the marginal cost of production in the "options" sheet is set to a nonzero value, these cells calculate the discounted cost of delivery and marginal cost of production.

Column BA displays country-by-country totals for the three calculations described above.

Column BB calculates the country-by-country cost effectiveness at delivery cost by dividing the total discounted cost by the total discounted DALYs saved.

Column BC sets a flag to 1 if it the cost per DALY in column BB exceeds the threshold specified.

14. HIV-AIDS NEW COHORTS

This purpose of this worksheet is to obtain the expected DALY burden of HIV-AIDS that would be relieved by vaccination over the lifetime of the typical newly born person in a country, given the duration of protection offered by the vaccine. Note that the calculation assumes that ten year olds are vaccinated rather than newborns, so the results on this sheet do not directly enter into the calculations. Default parameters are set for an ideal vaccine that would prevent mother to infant transmission of HIV/AIDS. If a vaccine would not do this or would only prevent transmission in breast milk, the user should change the "scaling factor for benefits ages 0-4" parameter.

14.1 DERIVATION OF BURDEN BY COUNTRY

This worksheet first displays the number of HIV positive individuals and proportion of HIV positive individuals from the 'hiv-aids cases' page for each country (columns D and F, respectively).

Then estimates for the distribution of DALY burden by sex and age group are calculated. Murray and Lopez (1996a) provide 1990 data on male/female and age group burden of disease according to their regional categories (Murray and Lopez, 1996a, Annex Table 9, pages 541, 545, 549, 553, 557, 561, 565, and 569).

Columns G through N assign each country the Murray and Lopez regional data with accordance to their regional codes. Columns O through V convert the regional numbers into proportions. In the absence of more detailed data, the regional proportions are used as the best estimate for country-level proportions of burden by sex and age.

Column W lists the 1999 regional burden of HIV/AIDS figures (in DALYs) from the World Health Report (WHO 2000), Statistical Annex Table 4. (The data appear in column Z in rows 190 to 203. The numbers are listed according to WHO's categories and sub-categories based on region and mortality stratum.)

In column X, an estimate of a country's DALY burden of HIV/AIDS is derived by multiplying the WHO regional total by the country's proportion of burden (from the hiv-aids cases page). To get country burden by sex in Y and Z, the country burden (in X) is multiplied by that country's regional proportion of burden by sex (in P and Q).

14.2 NEW COHORT DALY BURDEN

14.2.1 FORMULA FOR DALY BURDEN

In AA to AE, the burden per person of HIV/AIDS is found in the age categories 0-4, 5-14, 15-44, 45-59, and 60+ years old (these are the categories given by Murray and Lopez). The country burden is multiplied by the age category's share of burden in the country's region. Then this number is divided by the proportion of the age group in the total country population to obtain an average burden per person in the given age group.

Then the worksheet performs the steps necessary to calculate the lifetime burden for new cohorts. The lifetime burden for new cohorts can be interpreted as the discounted average number of disability-adjusted life years lost due to HIV/AIDS for a person born in a particular country. In general, Lifetime new cohort burden= burden 0-4 + burden 0-4 /(1+r) + burden 0-

4/[(1+r)^2] + burden 0-4/[(1+r)^3] + burden 0-4/[(1+r)^4] + burden 5-14/[(1+r)^5] + burden 5-14/[(1+r)^6] + … + burden country's last age group /[(1+r)^country life expectancy], where r is the real discount rate and burden i is the burden per person of age group i (i=0-4, 5-14, 15-44, 45-59, 60+). The DALY burden alleviated by the vaccine can be calculated by summing these terms over the periods during which the vaccine is effective. The results of this calculation are displayed in column AF.

To make this calculation easier, the new cohort DALY burden is broken apart by age group and the results are summed for each age group. In concrete terms,

Column BB= burden 0-4 + burden 0-4 /(1+r) + burden 0-4/[(1+r)^2] + burden 0-4/[(1+r)^3] + burden 0-4/[(1+r)^4]

Column BC= burden 5-14/[(1+r)^5] + burden 5-14/[(1+r)^6] + … + burden 5-14/[(1+r)^14]

Column BD= burden 15-44/[(1+r)^15] + burden 15-44/[(1+r)^16] + … + burden 5-14/[(1+r)^44]

Column BE= burden 45-59/[(1+r)^45] + burden 45-59/[(1+r)^46] + … + burden 45-59/[(1+r)^59]

Column BF= burden 60+/[(1+r)^60] + burden 60+/[(1+r)^61] + … + burden 60+ /[(1+r)^country life expectancy]

Please note that for some countries with a life expectancy less than 60, Column BF (or even BE and BF) will contain zeros. The lifetime burden is only calculated up to a country's life expectancy. In addition, columns will contain zeros if the vaccine's effectiveness elapses before the lower bound of the age range.

14.2.2 TECHNICAL IMPLEMENTATION OF FORMULA

Now the technical implementation of the above formulas will be explained. The form of the burden calculation for age group i (any column from BB to BF) is the following: =(-PV(real interest rate, years in annuity, payment ,,1))/((1+real interest rate)^years to discount)

The present value (PV) calculation requires four parameters: the real interest rate, the number of periods in the annuity, the “payment” made each period, and a dummy variable that indicates “payments” are due at the beginning of each period. See Microsoft Excel's Help for a more lengthy description of this function. The real interest rate comes from the options worksheet. The “payment” each period is the burden per person of age group i (in columns AA to AE). The number of periods in the annuity comes from two calculations: the “intermediate calculation” and “years in annuity.” Basically, the objective is to obtain the number of years within the given age interval after which vaccination begins. For example, for the 15-44 year old category, the answer is 30 if vaccination begins at birth (45-15=30). The “intermediate calculation” evaluates the number of years in a given age interval. The “years in annuity” calculation adjusts the value from the “intermediate calculation” in case vaccination has started after the given age period. This is the basic structure of the present value function.

Also, because the present value calculation is individually performed for each age period, the present value results must be adjusted in the following way. The present value DALYs for each age period is divided by [(1 + real interest rate) ^ years to discount]. In essence, “years to discount” gives the number of years between the age at which vaccination begins and the age at

which the given age period begins. Example: for the 15-44 year old category the answer is 15 if the vaccination begins at birth (15-0= 15). This adjustment is needed since the PV function has not accounted for the 15 years that have passed after vaccination begins and before the start of the 15-44 age group (i.e. the PV function has discounted such that the 15-44 age period were 15 years closer to present time).

Finally, the discounted DALYs are summed for the five age groups, which are BB to BF. The result is the DALY burden for new cohorts in AF.

One side note: this accounts for the fact that the life expectancy of countries varies widely. In many countries few people will live past 60 years of age. Therefore, in general, the population cannot accrue DALYs beyond 60 years of age. The "intermediate calculation II" corrects for this fact. It counts the number of years in an age period that fall below a country's life expectancy. Example: Suppose the 65-69 age category is considered. If the life expectancy in a country is 67, then the "intermediate calculation II" gives 2. If the life expectancy is 60, then the "intermediate calculation II" yields –5. If the life expectancy is 80, then it yields 5. The "years in annuity" calculation lists only the zero or positive values from the "intermediate calculation II." In this way, the calculations adjust for those countries that have a low average life expectancy. Further refinement of this work could incorporate heterogeneity in life expectancy within countries.

14.3 PREPARATION FOR CHILDREN AND OLD COHORT DALY BURDEN CALCULATIONS

Next, in preparation for the calculations for children and old cohorts, the present value calculations are performed in five year age intervals in columns CV to DK. The calculations that provide input parameters for the PV function (intermediate and years in annuity procedures) are the same as those for new cohorts (see BH to CU).

15. HIV-AIDS CHILDREN

This worksheet finds the average DALY burden of HIV/AIDS that would be relieved by vaccinating ten year olds.

Columns B through Q display the present value calculations that were obtained in columns CV to DK on the hiv-aids new cohorts worksheet. The discounted DALY burden that would be alleviated per ten year old, given the lag between infection and onset of disease, is calculated for an entire life span in columns AJ to AW. The total DALY burden that would be alleviated per ten year old, given the duration of protection offered by the vaccine, is displayed in column AX.

16. HIV-AIDS OLD COHORTS

This worksheet finds the average DALY burden of HIV/AIDS for an individual between the ages of 10 and 35. First, the average DALY burden that would be relieved given the duration of protection of the vaccine and the lag between infection and the onset of disease is found for each category. It is assumed that this person is in the middle of the age range; that is, of people that are between 20 and 25, all are 22.5 years old. To do this, the present value of burden that remains in the rest of her/his life for each span of five years in the lifetime is discounted. This value is set to zero if the protection offered by the vaccine elapses before the lower bound of the age range is attained. These discounted burden estimates are summed to get the lifetime burden of the median person in the age range. This procedure is performed for all age categories.

Then the weighted average of the age range DALY burdens for people from 10 to 35 is taken according to population distribution and divided by the proportion of 10 to 35 year olds in the country. This yields the average lifetime burden of HIV/AIDS per person between the ages 10 and 35 that would be alleviated by the vaccine, given the duration of protection it offers.

17. MALARIA

This worksheet is an intermediate calculation of the numbers of people vaccinated and DALYs saved, assuming 100% coverage.

17.1 NEW COHORTS IN COVERED COUNTRIES

Column B lists the burden of malaria in DALYs per new cohort from the malaria new cohorts worksheet. This number can be considered the marginal benefit of a successful intervention if the vaccine is perfectly effective.

Column C displays the number of births in one year in the country for covered countries which have disease prevalence. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column D finds the co-payments that a country will pay for new cohort vaccinations (unadjusted by the coverage rate). **NOTE: This function is currently inactive.**

Column E gives the number of DALYs that would be saved if all new cohorts in covered countries received the vaccination, given the duration of protection offered by the vaccine.

Column F records which countries receive new cohort vaccinations.

17.2 NEW COHORTS IN NON-COVERED COUNTRIES

Columns G through I are analogous to the previous section.

11.3 CHILDREN IN COVERED COUNTRIES

Column J lists the burden of malaria in DALYs that would be relieved per child from the malaria children worksheet. This number can be considered the marginal benefit of a successful vaccination, given the duration of protection offered by the vaccine.

Column K displays the number of 1 to 5 year olds in the country. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column L finds the co-payments that a country will pay for children vaccinations (unadjusted by the coverage rate). This option is currently inactive.

Column M gives the number of DALYs that would be saved if all children in covered countries received the vaccination, given the duration of protection offered by the vaccine.

Column N records which countries receive children vaccinations.

17.4 CHILDREN IN NON-COVERED COUNTRIES

Columns O to Q are analogous to the previous section.

17.5 OLD COHORTS (PREGNANT WOMEN) IN COVERED COUNTRIES

Column R lists the burden of malaria in DALYs per old cohort from the malaria old cohorts worksheet. Recall that the only adults immunized against malaria are women pregnant with their

first child. This number can be considered the marginal benefit of a successful untargeted vaccination, given the duration of protection of the vaccine.

Column S displays the number of women pregnant with their first child in the country. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column T finds the co-payments that a country will pay for old cohort vaccinations (unadjusted by the coverage rate). This function is currently inactive.

Column U gives the number of DALYs saved for those old cohorts that receive effective vaccinations. This is the DALY burden per old cohort times the number of vaccinations times the vaccine efficacy times the ratio of DALY burden (see notes for the options worksheet).

Column V records which countries receive old cohort vaccinations.

17.6 OLD COHORTS IN NON-COVERED COUNTRIES

Columns W to Y are analogous to the previous section.

17.7 COUNTRIES RECEIVING VACCINATIONS

Columns Z through AD list the covered countries receiving any vaccination, non-covered countries receiving any vaccination, any country receiving any vaccination, IDA eligibility for Commitment participating countries, and IDA eligibility for non-Commitment participating countries, respectively.

18. MALARIA COVERAGE

This worksheet obtains the number of vaccinations and DALYs saved for both covered and non-covered countries at the coverage rate specified in the “coverage” worksheet.

18.1 NEW COHORTS IN COVERED COUNTRIES

Column B lists the burden of malaria in DALYs per new cohort from the malaria new cohorts worksheet. This number can be considered the marginal benefit of a successful intervention if the vaccine is perfectly effective, and given the duration of protection offered by the vaccine.

Column C displays the number of births in one year in the country for covered countries which have disease prevalence, adjusted for the vaccine coverage rate. For more information on coverage rates, see the documentation for the “coverage” worksheet.

Column D finds the co-payments that a country will pay for new cohort vaccinations (adjusted by the coverage rate). **NOTE: This function is currently inactive.**

Column E gives the number of DALYs that would be saved at the coverage rate.

Column F records which countries receive new cohort vaccinations.

18.2 NEW COHORTS IN NON-COVERED COUNTRIES

Columns G through I are analogous to the previous section.

18.3 CHILDREN IN COVERED COUNTRIES

Column J lists the burden of malaria in DALYs per child from the malaria children worksheet. This number can be considered the marginal benefit of a successful vaccination, given the duration of protection of the vaccine.

Column K displays the number of 1 to 5 year olds in the country, adjusted for the vaccine coverage rate.

Column L finds the co-payments that a country will pay for children vaccinations (adjusted by the coverage rate). This option is currently inactive.

Column M gives the number of DALYs that would be saved at the coverage rates.

Column N records which countries receive children vaccinations.

18.4 CHILDREN IN NON-COVERED COUNTRIES

Columns O to Q are analogous to the previous section.

18.5 OLD COHORTS IN COVERED COUNTRIES

Column R lists the burden of malaria in DALYs per old cohort from the malaria old cohorts worksheet. Recall that the only adults immunized against malaria are women pregnant with their first child. This number can be considered the marginal benefit of a successful untargeted vaccination, given the duration of protection offered by the vaccine.

Column S displays the number of women pregnant with their first child in the country adjusted for the vaccine coverage rate.

Column T finds the co-payments that a country will pay for old cohort vaccinations (adjusted by the coverage rate). This function is currently inactive.

Column U gives the number of DALYs saved for those old cohorts that receive effective vaccinations. This is the DALY burden per old cohort times the number of vaccinations at the coverage rate times the vaccine efficacy times the ratio of DALY burden (see notes for the options worksheet).

Column V records which countries receive old cohort vaccinations.

18.6 OLD COHORTS IN NON-COVERED COUNTRIES

Columns W to Y are analogous to the previous section.

18.7 COUNTRIES RECEIVING VACCINATIONS

Columns Z through AD list the covered countries receiving any vaccination, non-covered countries receiving any vaccination, any country receiving any vaccination, IDA eligibility for Commitment participating countries, and IDA eligibility for non-Commitment participating countries, respectively.

19. MALARIA COST

This worksheet calculates the discounted sum of DALYs saved by the program in each country over a 50 year horizon, the number of vaccinations in each country in each year given the takeup rates, and the discounted sum of the costs of delivery in each country. It then flags countries for which vaccination would not be cost-effective relative to the $100 threshold at delivery cost.

Rows 5 to 189, Columns B to AY calculate the discounted DALYs saved in each year given the takeup path specified by the user. The calculation assumes a linear takeup path to the steady-state level for new cohorts. Vaccinations of children and old cohorts are distributed over the transition to the steady state. Future DALYs are discounted using the real discount rate.

Rows 197 to 381, Columns B to AY calculate the number of vaccinations in each country in each year given the takeup path specified by the user. The calculation assumes a linear takeup path to the steady-state level for new cohorts. Vaccinations of children and old cohorts are distributed over the transition to the steady state.

Rows 387 to 571, Columns B to AY calculate the discounted cost of delivery of vaccinations in each year given the takeup path specified by the user. If the marginal cost of production in the "options" sheet is set to a nonzero value, these cells calculate the discounted cost of delivery and marginal cost of production.

Column BA displays country-by-country totals for the three calculations described above.

Column BB calculates the country-by-country cost effectiveness at delivery cost by dividing the total discounted cost by the total discounted DALYs saved.

Column BC sets a flag to 1 if it the cost per DALY in column BB exceeds the threshold specified.

20. MALARIA NEW COHORTS

This purpose of this worksheet is to obtain the expected DALY burden of malaria for the typical newly born person in each country.

20.1 DERIVATION OF BURDEN BY COUNTRY

This worksheet first displays the country's share of regional malaria burden from the malaria cases page for each country (column D).

Then estimates for the distribution of DALY burden by sex and age group are calculated. Murray and Lopez (1996a) provide 1990 data on male/female and age group burden of disease according to their regional categories (The numbers are listed in a table located in E190. See Murray and Lopez (1996a), Annex Table 9, pages 541, 545, 549, 553, 557, 561, 565, and 569).

Columns E through Q assign each country the Murray and Lopez regional data with accordance to their regional codes. Unlike the case with HIV/AIDS and tuberculosis, the age group regional burden of malaria needs to be broken down further by sex. This is because only women pregnant with their first child are vaccinated as opposed to all adults between the ages 10 and 35.

Columns R through AD convert the regional numbers into proportions. In the absence of more detailed data, the regional proportions are used as the best estimate for country-level proportions of burden by sex and age.

Column AE lists the 1999 regional burden of malaria figures (in DALYs) from the World Health Report (WHO 2000), Statistical Annex Table 4. (The data appear in a table in column AH in rows 190 to 203. The numbers are listed according to WHO's categories and sub-categories based on region and mortality stratum, respectively.)

In column AF, an estimate of a country's DALY burden of malaria is estimated by multiplying the WHO regional total by the country's proportion of burden (from the malaria cases worksheet). To get country burden by sex in AG and AH, the country burden (in AF) is multiplied by that country's regional proportion of burden by sex (in S and T).

20.2 NEW COHORT DALY BURDEN

20.2.1 FORMULA FOR DALY BURDEN

In AI to AR, then the burden per person of malaria is found in the age categories 0-4, 5-14, 15-44, 45-59, and 60+ years old (these are the categories given by Murray and Lopez). The country burden is multiplied by the age category's share of burden in the country's region. Then this number is divided by the proportion of the age group in the total country population to obtain an average burden per person in the given age group.

The worksheet then goes through the steps necessary to calculate the lifetime burden for new cohorts. The lifetime burden for new cohorts can be interpreted as the discounted average number of disability-adjusted life years lost due to malaria for a person born in a particular country. In general,

Lifetime new cohort burden= burden 0-4 + burden 0-4 /(1+r) + burden 0-4/[(1+r)^2] + burden 0-4/[(1+r)^3] + burden 0-4/[(1+r)^4] + burden 5-14/[(1+r)^5] + burden 5-14/[(1+r)^6] + … + burden country's last age group /[(1+r)^country life expectancy], where r is the real discount rate and burden i is the burden per person of age group i (i=0-4, 5-14, 15-44, 45-59, 60+). The DALY burden alleviated by the vaccine can be calculated by summing these terms over the periods during which the vaccine is effective. The result of this calculation is displayed in column AS.

To make this calculation easier, the lifetime new cohort burden are broken apart by age group and the results are summed for each age group. In concrete terms,

Column BO= burden 0-4 + burden 0-4 /(1+r) + burden 0-4/[(1+r)^2] + burden 0-4/[(1+r)^3] + burden 0-4/[(1+r)^4]

Column BP= burden 5-14/[(1+r)^5] + burden 5-14/[(1+r)^6] + … + burden 5-14/[(1+r)^14]

Column BQ= burden 15-44/[(1+r)^15] + burden 15-44/[(1+r)^16] + … + burden 5-14/[(1+r)^44]

Column BR= burden 45-59/[(1+r)^45] + burden 45-59/[(1+r)^46] + … + burden 45-59/[(1+r)^59]

Column BS=burden 60+/[(1+r)^60] + burden 60+/[(1+r)^61] + … + burden 60+ /[(1+r)^country life expectancy]

Please note that for some countries with a life expectancy less than 60, Column BS (or even BS and BR) will contain zeros. The lifetime burden is calculated up to a country's life expectancy.

Columns will also contain zeros if the protection offered by the vaccine elapses before the lower bound of the age range is attained.

20.2.2 TECHNICAL IMPLEMENTATION OF FORMULA

Now the technical implementation of the above formulas will be explained. The form of the burden calculation for age group i (any column from BO to BS) is the following: =(-PV(real interest rate, years in annuity, payment ,,1))/((1+real interest rate)^years to discount)

The present value (PV) calculation requires four parameters: the real interest rate, the number of periods in the annuity, the “payment” made each period, and a dummy variable that “payments” are due at the beginning of each period. See Microsoft Excel's Help for a more lengthy description of this function. The real interest rate comes from the options worksheet, Row 8. The “payment” each period is the burden per person of age group i (in columns AI to AR). The number of periods in the annuity comes from two calculations: the “intermediate calculation” and “years in annuity.” Basically, it is necessary to obtain the number of years within the given age interval after which vaccination begins. For example, for the 15-44 year old category, the answer is 30 if vaccination begins at birth (45-15=30). The “intermediate calculation” evaluates the number of years in a given age interval. The “years in annuity” calculation adjusts the value from the “intermediate calculation” in case vaccination has started after the given age period. This is the basic structure of the present value function.

Also, because the present value calculation is individually performed for each age period, the present value results must be adjusted in the following way. The present value DALYs for each

age period are divided by [(1 + real interest rate) ^ years to discount]. In essence, “years to discount” gives the number of years between the age at which vaccination begins and the age at which the given age period begins. Example: for the 15-44 year old category the answer is 15 if the vaccination begins at birth (15-0= 15). This adjustment is necessary as the PV function has not accounted for the 15 years that have passed after vaccination begins and before the start of the 15-44 age group (i.e. the PV function has discounted such that the 15-44 age period were 15 years closer to present time).

Finally, the discounted DALYs are summed for the five age groups, which are BO to BS. The result is the lifetime burden for new cohorts in AS.

One side note: the spreadsheet accounts for the fact that the life expectancy of countries varies widely. In many countries few people will live past 60 years of age; therefore, in general, the population cannot accrue DALYs beyond 60 years of age. The “intermediate calculation II” corrects for this fact. It counts the number of years in an age period that fall below a country’s life expectancy. Example: Suppose the 65-69 age category is considered. If the life expectancy in a country is 67, then the “intermediate calculation II” gives 2. If the life expectancy is 60, then the “intermediate calculation II” yields –5. If the life expectancy is 80, then it yields 5. The “years in annuity” calculation lists only the zero or positive values from the “intermediate calculation II.” In this way, the calculations adjust for those countries that have a low average life expectancy. Further refinement of this work could incorporate heterogeneity in life expectancy within countries.

20.3 PREPARATION FOR CHILDREN AND OLD COHORTS LIFETIME BURDEN CALCULATIONS

Next, in preparation for the calculations for children and old cohorts, the present value calculations are performed in five year age intervals in columns DI to DX. The calculations that provide input parameters for the PV function (intermediate and years in annuity procedures) are the same as those for new cohorts (see BU to DH).

21. MALARIA CHILDREN

This worksheet finds the DALY burden of malaria for a child between the ages of 0 and 5 that would be alleviated by vaccination, given the duration of protection offered by the vaccine. Columns B through Q display the present value calculations based on saving the average of the burden per person for males and females age 0 to 4. Since the data relates to five-year ranges, it is assumed that all individuals are in the middle of their particular age range. Thus, it is assumed that all children between the ages of 0 and 5 in a country are all 2.5 years old.

The discounted burden per person in the 0-4 age range is calculated for an entire life span. Values are set to zero if the protection offered by the vaccine elapses before the lower bound of the age range is attained. These discounted burden numbers are summed to get the lifetime burden of malaria for a child between the ages of 0 and 5 that would be alleviated by vaccination.

22. MALARIA OLD COHORTS

This worksheet finds the average DALY burden of malaria for pregnant women between the ages of 15 and 50 that would be alleviated by vaccination, given the duration of protection offered by the vaccine. First, the average DALY burden is found for an individual in each age category. It is assumed that this person is in the middle of the age range; that is, of people that are between 20 and 25, all are 22.5 years old. To do this, the present value of the DALY burden that remains in the rest of her life for each span of five years in the lifetime is discounted. These values are set to zero if the protection of the vaccine has elapsed before the lower bound of the age range is attained. These discounted burden estimates are summed to get the DALY burden of the median person in the age range. This procedure is performed for all age categories.

Then the weighted average of the age range DALY burdens is taken for pregnant women from 15 to 50 according to the fertility distribution. This yields the average burden of malaria per pregnant woman between the ages 15 and 50 that would be alleviated by vaccination.

23. TB

This worksheet is an intermediate calculation of the numbers of people vaccinated and DALYs saved, assuming 100% coverage.

23.1 NEW COHORTS IN COVERED COUNTRIES

Column B lists the burden of tuberculosis in DALYs per new cohort from the tb new cohorts worksheet. This number can be considered the marginal benefit of a successful intervention if the vaccine is perfectly effective, given the duration of protection offered by the vaccine.

Column C displays the number of births in one year in the country for covered countries which have disease prevalence. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column D finds the co-payments that a country will pay for new cohort vaccinations (unadjusted by the coverage rate). **NOTE: This function is currently inactive.**

Column E gives the number of DALYs that would be saved if all new cohorts in covered countries received the vaccination, given the duration of protection offered by the vaccine.

Column F records which countries receive new cohort vaccinations.

23.2 NEW COHORTS IN NON-COVERED COUNTRIES

Columns G through I are analogous to the previous section.

23.3 CHILDREN IN COVERED COUNTRIES

Column J lists the burden of tuberculosis in DALYs per child from the tb children worksheet. This number can be considered the marginal benefit of a successful vaccination, given the duration of protection offered by the vaccine.

Column K displays the number of 1 to 10 year olds in the country. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column L finds the co-payments that a country will pay for children vaccinations (unadjusted by the coverage rate). This option is currently inactive.

Column M gives the number of DALYs that would be saved if all children in covered countries received the vaccination, given the duration of protection offered by the vaccine.

Column N records which countries receive children vaccinations.

23.4 CHILDREN IN NON-COVERED COUNTRIES

Columns O to Q are analogous to the previous section.

23.5 OLD COHORTS IN COVERED COUNTRIES

Column R lists the burden of tuberculosis in DALYs per old cohort from the tb old cohorts worksheet. This number can be considered the marginal benefit of a successful untargeted vaccination, given the duration of protection offered by the vaccine.

Column S displays the number of 10 to 35 year olds in the country. This number is adjusted for the vaccine coverage rate on a subsequent worksheet.

Column T finds the co-payments that a country will pay for old cohort vaccinations (unadjusted by the coverage rate). This function is currently inactive.

Column U gives the number of DALYs saved for those old cohorts that receive effective vaccinations. This is the DALY burden per old cohort times the number of vaccinations times the vaccine efficacy times the ratio of DALY burden (see notes for the options worksheet).

Column V records which countries receive old cohort vaccinations.

23.6 OLD COHORTS IN NON-COVERED COUNTRIES

Columns W to Y are analogous to the previous section.

23.7 COUNTRIES RECEIVING VACCINATIONS

Columns Z through AD list the covered countries receiving any vaccination, non-covered countries receiving any vaccination, any country receiving any vaccination, IDA eligibility for

Commitment participating countries, and IDA eligibility for non-Commitment participating countries, respectively.

24. TB COVERAGE

This worksheet obtains the number of vaccinations and DALYs saved for both covered and non-covered countries at the coverage rate specified in the “coverage” worksheet.

24.1 NEW COHORTS IN COVERED COUNTRIES

Column B lists the DALY burden of tuberculosis in DALYs per new cohort from the tb new cohorts worksheet. This number can be considered the marginal benefit of a successful intervention if the vaccine is perfectly effective, given the duration of protection offered by the vaccine.

Column C displays the number of births in one year in the country for covered countries which have disease prevalence. This number is adjusted for the vaccine coverage rate. For more information on coverage rates, see the documentation for the “coverage” worksheet.

Column D finds the co-payments that a country will pay for new cohort vaccinations (adjusted by the coverage rate). **NOTE: This function is currently inactive.**

Column E gives the number of DALYs that would be saved at the coverage rates, given the duration of protection offered by the vaccine, and vaccine efficacy.

Column F records which countries receive new cohort vaccinations.

24.2 NEW COHORTS IN NON-COVERED COUNTRIES

Columns G through I are analogous to the previous section.

24.3 CHILDREN IN COVERED COUNTRIES

Column J lists the DALY burden of tuberculosis in DALYs per child from the tb children worksheet. This number can be considered the marginal benefit of a successful vaccination, given the duration of protection offered by the vaccine.

Column K displays the number of 1 to 10 year olds in the country. This number is adjusted for the vaccine coverage rate.

Column L finds the co-payments that a country will pay for children vaccinations (adjusted by the coverage rate). This option is currently inactive.

Column M gives the number of DALYs that would be saved at the coverage rates, given the duration of protection offered by the vaccine, and vaccine efficacy.

Column N records which countries receive children vaccinations.

24.4 CHILDREN IN NON-COVERED COUNTRIES

Columns O to Q are analogous to the previous section.

24.5 OLD COHORTS IN COVERED COUNTRIES

Column R lists the DALY burden of tuberculosis in DALYs per old cohort from the tb old cohorts worksheet. This number can be considered the marginal benefit of a successful untargeted vaccination, given the duration of protection offered by the vaccine.

Column S displays the number of 10 to 35 year olds in the country adjusted for the vaccine coverage rate.

Column T finds the co-payments that a country will pay for old cohort vaccinations (adjusted by the coverage rate). This function is currently inactive.

Column U gives the number of DALYs saved for those old cohorts that receive effective vaccinations. This is the DALY burden per old cohort times the number of vaccinations at the coverage rate times the vaccine efficacy times the ratio of DALY burden (see notes for the options worksheet).

Column V records which countries receive old cohort vaccinations.

24.6 OLD COHORTS IN NON-COVERED COUNTRIES

Columns W to Y are analogous to the previous section.

24.7 COUNTRIES RECEIVING VACCINATIONS

Columns Z through AD list the covered countries receiving any vaccination, non-covered countries receiving any vaccination, any country receiving any vaccination, IDA eligibility for

Commitment participating countries, and IDA eligibility for non-Commitment participating countries, respectively.

25. TB COST

This worksheet calculates the discounted sum of DALYs saved by the program in each country over a 50 year horizon, the number of vaccinations in each country in each year given the takeup rates, and the discounted sum of the costs of delivery in each country. It then flags countries for which vaccination would not be cost-effective relative to the $100 threshold at delivery cost.

Rows 5 to 189, Columns B to AY calculate the discounted DALYs saved in each year given the takeup path specified by the user. The calculation assumes a linear takeup path to the steady-state level for new cohorts. Vaccinations of children and old cohorts are distributed over the transition to the steady state. Future DALYs are discounted using the real discount rate.

Rows 197 to 381, Columns B to AY calculate the number of vaccinations in each country in each year given the takeup path specified by the user. The calculation assumes a linear takeup path to the steady-state level for new cohorts. Vaccinations of children and old cohorts are distributed over the transition to the steady state.

Rows 387 to 571, Columns B to AY calculate the discounted cost of delivery of vaccinations in each year given the takeup path specified by the user. If the marginal cost of production in the "options" sheet is set to a nonzero value, these cells calculate the discounted cost of delivery and marginal cost of production.

Column BA displays country-by-country totals for the three calculations described above.

Column BB calculates the country-by-country cost effectiveness at delivery cost by dividing the total discounted cost by the total discounted DALYs saved.

Column BC sets a flag to 1 if it the cost per DALY in column BB exceeds the threshold specified.

26. TB NEW COHORTS

This purpose of this worksheet is to obtain the expected DALY burden of tuberculosis for the typical newly born person in each country.

26.1 DERIVATION OF BURDEN BY COUNTRY

This worksheet first displays each country's tb cases and share of regional burden from the tb cases page for each country (columns D and F, respectively).

Then estimates of the distribution of DALY burden by sex and age group are calculated. Murray and Lopez (1996a) provide 1990 data on male/female and age group burden of disease according to their regional categories (Murray and Lopez (1996a), Annex Table 9, pages 541, 545, 549, 553, 557, 561, 565, and 569).

Columns G through N assign each country the Murray and Lopez regional data with accordance to their regional codes. Columns O through V convert the regional numbers into proportions. In the absence of more detailed data, the regional proportions are used as the best estimate for country-level proportions of burden by sex and age.

Column W lists the 1999 regional burden of tuberculosis (in DALYs) from the World Health Report (WHO 2000), Statistical Annex Table 4. (The data appear in column Z in rows 190 to 203. The numbers are listed according to WHO's categories and sub-categories based on region and mortality stratum.)

In column X, an estimate of a country's DALY burden of tuberculosis is derived by multiplying the WHO regional total by the country's proportion of burden (from the tb cases worksheet). To get country burden by sex in Y and Z, the country burden (in X) is multiplied by that country's regional proportion of burden by sex (in P and Q).

26.2 NEW COHORTS LIFETIME BURDEN

26.2.1 FORMULA FOR LIFETIME BURDEN

In AA to AE, then the burden per person of tuberculosis is found in the age categories 0-4, 5-14, 15-44, 45-59, and 60+ years old (these are the categories given by Murray and Lopez). The country burden is multiplied by the age category's share of burden in the country's region. This number is then divided by the proportion of the age group in the total country population to obtain an average burden per person in the given age group.

The worksheet then goes through the steps necessary to calculate the lifetime burden for new cohorts. The burden for new cohorts can be interpreted as the discounted average number of disability-adjusted life years lost due to tuberculosis for a person born in a particular country. In general, Lifetime new cohort burden=burden 0-4 + burden 0-4 /(1+r) + burden 0-4/[(1+r)^2] + burden 0-4/[(1+r)^3] + burden 0-4/[(1+r)^4] + burden 5-14/[(1+r)^5] + burden 5-14/[(1+r)^6] + … + burden country's last age group /[(1+r)^country life expectancy], where r is the real discount rate and burden i is the burden per person of age group i (i=0-4, 5-14, 15-44, 45-59, 60+). The DALY burden alleviated by the vaccine can be calculated by summing these terms over the periods during which the vaccine is effective. The results of this calculation are displayed in column AF.

To make this calculation easier, the lifetime new cohort burden is broken apart by age group and the results are summed for each age group. In concrete terms,

Column BB= burden 0-4 + burden 0-4 /(1+r) + burden 0-4/[(1+r)^2] + burden 0-4/[(1+r)^3] + burden 0-4/[(1+r)^4]

Column BC= burden 5-14/[(1+r)^5] + burden 5-14/[(1+r)^6] + … + burden 5-14/[(1+r)^14]

Column BD= burden 15-44/[(1+r)^15] + burden 15-44/[(1+r)^16] + … + burden 5-14/[(1+r)^44]

Column BE= burden 45-59/[(1+r)^45] + burden 45-59/[(1+r)^46] + … + burden 45-59/[(1+r)^59]

Column BF= burden 60+/[(1+r)^60] + burden 60+/[(1+r)^61] + … + burden 60+ /[(1+r)^country life expectancy]

Please note that for some countries with a life expectancy less than 60, Column BF (or even BE and BF) will contain zeros. The lifetime burden is only calculated up to a country's life expectancy. In addition, cells will contain zeros if the protection offered by the vaccine elapses before the lower bound of the age range is attained.

26.2.2 TECHNICAL IMPLEMENTATION OF FORMULA

Now the technical implementation of the above formulas will be explained. The form of the burden calculation for age group i (any column from BB to BF) is the following: =(-PV(real interest rate, years in annuity, payment ,,1))/((1+real interest rate)^years to discount)

The present value (PV) calculation requires four parameters: the real interest rate, the number of periods in the annuity, the “payment” made each period, and a dummy variable that “payments” are due at the beginning of each period. See Microsoft Excel's Help for a more lengthy description of this function. The real interest rate comes from the options worksheet, Row 8.

The “payment” each period is the burden per person of age group i (in columns AA to AE). The number of periods in the annuity comes from two calculations: the “intermediate calculation” and “years in annuity.” Basically, the objective is to obtain the number of years within the given age interval after which vaccination begins. For example, for the 15-44 year old category, the answer is 30 if vaccination begins at birth (45-15=30). The “intermediate calculation” evaluates the number of years in a given age interval. The “years in annuity” calculation adjusts the value from the “intermediate calculation” in case vaccination has started after the given age period. This is the basic structure of the present value function.

Also, because the present value calculation is individually performed for each age period, the present value results must be adjusted in the following way. The present value DALYs for each age period are divided by [(1 + real interest rate) ^ years to discount]. In essence, “years to discount” gives the number of years between the age at which vaccination begins and the age at which the given age period begins. Example: for the 15-44 year old category the answer is 15 if the vaccination begins at birth (15-0= 15). This adjustment is necessary since the PV function has not accounted for the 15 years that have passed after vaccination begins and before the start of the 15-44 age group (i.e. the PV function has discounted such that the 15-44 age period were 15 years closer to present time).

Finally, the discounted DALYs are summed for the five age groups, which are BB to BF. The result is the lifetime burden for new cohorts in AF.

One side note: the calculations account for the fact that the life expectancy of countries varies widely. In many countries few people will live past 60 years of age; therefore, in general, the population cannot accrue DALYs beyond 60 years of age. The "intermediate calculation II" corrects for this fact. It counts the number of years in an age period that fall below a country's life expectancy. Example: Suppose the 65-69 age category is considered. If the life expectancy in a country is 67, then the "intermediate calculation II" gives 2. If the life expectancy is 60, then the "intermediate calculation II" yields –5. If the life expectancy is 80, then it yields 5. The "years in annuity" calculation lists only the zero or positive values from the "intermediate calculation II." In this way, the spreadsheet adjusts for those countries that have a low average life expectancy. Further refinement of this work could incorporate heterogeneity in life expectancy within countries.

26.3 PREPARATION FOR CHILDREN AND OLD COHORTS LIFETIME BURDEN CALCULATIONS

Next, in preparation for the calculations for children and old cohorts, the present value calculations are performed in five year age intervals in columns CV to DK. The calculations that provide input parameters for the PV function (intermediate and years in annuity procedures) are the same as those for new cohorts (see BH to CU).

27. TB CHILDREN

This worksheet finds the average DALY burden of tuberculosis that would be relived by immunizing a child between the ages of 1 and 10, given the duration of protection offered by the vaccine.

Columns B through Q display the present value calculations from columns CV to DK on tb new cohorts. Since the data pertain to five-year ranges, it is assumed that all individuals are in the middle of their particular age range. Thus, it is assumed that all children between the ages of 5 and 10 in a country are all 7.5 years old.

The discounted burden per person in each age range (0-4 and 5-10) is calculated for an entire life span. These values are set to zero if the protection offered by the vaccine elapses before the lower bound of the age range is attained. A weighted average of the age category burden figures is taken according to the population distribution in each country and divide by the proportion of 1-10 year olds in the country to obtain the DALY burden that would be alleviated per child.

28. TB OLD COHORTS

This worksheet finds the average DALY burden of tuberculosis for an individual between the ages of 10 and 35. First, the average DALY burden is found for an individual in each age category. It is assumed that this person is in the middle of the age range; that is, of people that are between 20 and 25, all are 22.5 years old. To do this, the present value of burden that remains in the rest of her/his life for each span of five years in the lifetime is discounted. These values are set to zero if the protection offered by the vaccine elapses before the lower bound of the age range is attained. These discounted burden estimates are summed to get the lifetime burden of the median person in the age range. This procedure is performed for all age categories.

Then the weighted average of the age range DALY burdens is taken for people from 10 to 35 according to population distribution and divided by the proportion of 10 to 35 year olds in the country. This yields the average DALY burden of tuberculosis per person between the ages 10 and 35.

29. DPT3

This worksheet calculates the default coverage rates for new cohorts based on 2002 measles, DPT1 (diphtheria, pertussis, tetanus first dose, or DPT3 (diphtheria, pertussis, tetanus third dose) coverage rate data. It also calculates the default coverage rates for pregnant women based on the tetanus toxoid (TT2) rates (for the case of malaria).

Columns F, H, J and L contain the data on coverage rates. If data are missing for a country, they are either estimated as the region low, using the WHO region and mortality codes in column F. Columns G, I, K and M contain flags that are set to 1 if the data are estimated. Column N contains the new cohorts default coverage rate, and column P contains the pregnant women default coverage rate.

30. COVERAGE

This worksheet calculates the coverage rates based on the user-entered inputs and the DPT3 data on the “DPT3” sheet.

The user can specify the new cohort coverage rates to be the 2002 measles, DPT1 or DPT3 rates plus or minus a fixed number of percentage points (rates in individual countries are capped at 100 percent and cannot go below 0%), or enter a single rate for all countries. New cohort takeup rates are displayed in column C.

The coverage rate for children is displayed in column D.

The coverage ratse for old cohorts are displayed in column E. For the case of malaria, users can specify these rates to be the 2002 TT2 rates plus or minus a fixed number of percentage points, or enter a single rate for all countries.

31. TIMEPATH

The timepath worksheet calculates the total number of vaccinations in each year for a 50 year horizon, when the high price purchases end, the total cost of vaccinations, and the cost effectiveness of the program in terms of cost per DALY saved.

Columns B through D contain the number of vaccinations in each year for HIV/AIDS, malaria, and tuberculosis respectively. The cumulative sum of these vaccinations is displayed in columns H through J.

Columns K through M contain a flag which is 1 if the total number of doses purchased surpasses the number specified by the program.

In the last year of high-price purchases, some purchases will be at the high price (before the limit of people covered by the program is reached) and some will be at the low price. Columns N through P contain the number of high-price doses in the last year of the program.

Columns T through V contain the discounted cost of vaccinations in each year, including the price paid and the delivery costs. These costs are discounted at the real discount rate and measured in current (2004) dollars.

Columns W through Y contain the total cost per DALY saved.

Columns Z to AB display the number of years until the end of the program.

Columns AI through AK display the cost of vaccinations in the absence of a price commitment, discounted to the date of development of the vaccine. This calculation assumes that the profile of takeup rates would be the same as in the case with the price commitment, once the vaccine was developed and adoption of the vaccine began. It also assumes that in the absence of a price commitment, the price of the vaccine would be $2 for the first ten years and $1 thereafter. This option is only available in the version of the spreadsheet for special applications, and does not appear in the basic Vaccine Spreadsheet.

Columns AL through AN display the total cost in the scenario without a price commitment.

Columns AO through AQ display the total cost in the scenario with a price commitment.

Columns AR through AT display the cost per additional DALY that would be saved by a price commitment, given the number of years that development and adoption of the vaccine would be advanced by the commitment. In order to do this, all quantities are discounted to the date that the vaccine would be developed in the presence of a price commitment. Then, the cost per additional DALY saved is calculated as (discounted cost of purchase and delivery with price commitment – discounted cost of purchase and delivery in the absence of a price commitment)/ (discounted DALYs saved with price commitment – discounted DALYs saved in the absence of a price commitment).

32. REVENUES

This sheet calculates the net present value (NPV) of revenues from purchases made at the high-price under the vaccine commitment, and also at the low price after the end of the program.

The revenues from program sales in each year up to 50 years are displayed in Columns A through C. Discounted revenues, discounted at the high-risk rate (comparable to the average return on the stock market), are displayed in Columns E through G. The total NPV of revenues for the vaccines are displayed in columns H through J.

Analogous calculations for the low price doses appear in columns K through S – these revenues are not included in the figures reported by the GUI.

33. GUI DEFAULTS

This sheet contains the default values for the “base case” which appears in the GUI at startup.

These values should not be modified by the user.

34. HELPTEXTS

This sheet contains help texts which can be accessed through the “Help” tab on the GUI. These cells should not be modified.

35. GUI

This sheet contains a range of values necessary for the operation of the GUI and values in this sheet should not be directly modified. The GUI can be restarted by pressing the Command Button on this sheet.

36. GUI RESULTS

This sheet contains the main results of the spreadsheet and simply facilitates output to the GUI.