challenge paper

INFECTIOUS DISEASE

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INFECTIOUS DISEASE, INJURY AND REPRODUCTIVE HEALTH[1]

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by

Dean T. Jamison, Prabhat Jha, Ramanan Laxminarayan and Toby Ord

This paper identifies key priorities for the control of infectious disease, injury and reproductive problems for the Copenhagen Consensus 2012 (CC12). It draws directly upon the disease control paper (Jamison, Bloom and Jha, 2008) from Copenhagen Consensus 2008 and the AIDS vaccine paper for the Copenhagen Consensus Rethink HIV project (Hecht and Jamison, 2011). This paper updates the evidence and adjusts the conclusions of the previous work in light of subsequent research and experience. For CC12 noncommunicable diseases are being treated in a separate paper (Jha, Nugent, Verguet, Bloom and Hum, 2012) that complements this one.

All these papers build on the results of the Disease Control Priorities Project (DCPP).[6] The DCPP engaged over 350 authors and estimated the cost-effectiveness of 315 interventions. These estimates vary a good deal in their thoroughness and in the extent to which they provide regionally-specific estimates of both cost and effectiveness. Taken as a whole, however, they represent a comprehensive canvas of disease control opportunities.[7] We will combine this body of knowledge with the results from research and operational experience in the subsequent four years.

The DCPP concluded that some interventions are clearly low priority. Others are worth doing but either address only a relatively small proportion of disease burden or simply prove less

[6] The DCPP was a joint effort, extending over 4 years, of the Fogarty International Center of the U.S. National Institutes of Health, the World Bank, and the World Health Organization with financial support from the Bill & Melinda Gates Foundation. While the views and conclusions expressed in this paper draw principally on the DCPP, others might draw different broad conclusions. In particular views expressed in this paper are not necessarily those of any of the sponsoring organizations.

[7] See Jamison et al (2006) and Laxminarayan et al (2006).

attractive than a few key interventions. This paper identifies 6 key interventions in terms of their cost-effectiveness, the size of the disease burden they address, the amount of financial protection they provide, their feasibility of implementation and their relevance for development assistance budgets. The resulting 'dashboard' of indicators underpins overall judgments of priority. Separate but related papers for CC12 deal with malnutrition (Hoddinott et al, 2012) with water and sanitation (Rijsberman and Zwane, 2012) with population growth (Kohler, 2012) and with education (Orazem, 2012).

Before turning to the substance of the paper it is worth briefly stating our perspectives on the roles of the state and of international development assistance in financing health interventions. There are major positive externalities associated with control of many infections and there are important public goods aspects to health education and R&D. On one view the rationale for state finance is to address these market failures and to address needs of vulnerable groups. Our view is rather different.

Among the high-income OECD countries, only the U.S. focuses public finance on vulnerable groups—the poor and the elderly. Other OECD countries provide universal public finance for the (generally comprehensive) set of health interventions that the public sector finance, at all. Private finance is explicitly crowded out by public action, even for purely private clinical services (such as setting fractures) which most individuals would be willing and able to pay for themselves (perhaps with privately financed insurance). Arrow's (1963) classic paper points to potential theoretical justifications for choosing universal public finance. The poor outcomes of the U.S. system with respect to health indicators, financial protection and total costs

(and even with respect to public sector expenditures as a percent of GDP) provide empirical evidence suggestive of the merits of universal public finance.[8]

The perspective of this paper is that of universal public finance adopted by the non-U.S. OECD countries[9]. From this perspective one is seeking to maximize health gains (or a broader objective function) subject to a public sector budget constraint without regard for the presence of public goods or externalities (except insofar as they affect aggregate health) and by addressing the needs of the poor through selecting interventions for universal finance that are of particular importance to the poor. No costs then accrue to targeting and no disincentives to work effort result from the potential loss of income-related health benefits. We further view the political economy of universalism as enhancing sustainability. Reasonable people may disagree, however, on the merits of universal public finance but even in that case private purchasers of health or health insurance may find cost-benefit information relevant to choice.

Our view of the role of international development assistance in health does, in contrast, centrally involve externalities and international public goods. Cross-border transmission of infection or drug resistance involves important negative externalities and R&D constitutes a public good that has been enormously important in health. Two of our five priorities reflect those concerns. Likewise, facilitating diffusion of best practice through development assistance or price incentives can be viewed as correction of temporary price distortions and hence a reasonable purpose of aid. (Foreign direct investment in the private sector provides an analogy, whereby international investors bring best practices along with their financial investments.) When we discuss the "best buys" in health we do so principally from the perspective of national

[8] See Barr (2001) and Lindert (2004) for more extended discussions.
[9] If implemented, the Obama health care reform will align the U.S. system much more closely with those of other high income countries.

authorities but, for interventions that may be of importance to development assistance beyond their importance from a national perspective, we point to the role of development assistance.

Section 1 of the paper documents the enormous success in much of the world in the past 40 years in improving health in low- and middle-income countries. Its conclusion is that future investments can build on past successes—increasing confidence in the practical feasibility of major additional gains in disease control. Section 2 summarizes evidence that health gains have had major economic and welfare impact, and Section 3 uses this economic context to describe the methods used for the cost-benefit analyses reported. Sections 4, 5 and 6 discuss problems and opportunities in reproductive and child health, HIV/AIDS and tuberculosis, respectively. Section 7 concludes by identifying the 6 most attractive solutions and presenting (very approximate) cost-benefit analyses for them. Our benefit:cost estimates are placed on a 'dashboard' including other information relevant for priority setting. This paper emphasizes, although not exclusively, opportunities relevant to low-income countries.

1. PROGRESS AND CHALLENGES

Health conditions improved markedly throughout the world during most of the second half of the 20th century and this section begins by highlighting those achievements. Nonetheless major problems remain in the early 21st century. Parts of the world have failed to keep up with the remarkable progress in other parts; declines in mortality and fertility had led to an increasing importance of noncommunicable disease; and the now maturing problem of HIV/AIDS has rapidly become prominent in many countries. Addressing these problems within highly constrained budgets will require hard choices, even in the current era of expanding domestic

health spending and overseas development assistance on health. This section concludes by reviewing these challenges.

1.1 Progress

Table 1 shows progress in life expectancy by UN region between 1960 and 2010. For the first three decades of this period, progress was remarkably fast—a gain of 4.2 years in life expectancy per decade on average, in the less developed countries, albeit with substantial regional variation. Progress continued between 2000 and 2010 but at a slower pace. In addition to overall progress, since 1950 life expectancy in the median country has steadily converged toward the (steadily growing) maximum across all countries and cross-country differences have decreased markedly (Oeppen and Vaupel, 2002; Vallin and Mesle, 2010). This reduction in inequality in health contrasts with long-term *increases* in income inequality between and within countries. Yet despite the magnitude of global improvements, many countries and populations have failed to share in the overall gains or have even fallen behind. Some countries—for example, Sierra Leone—remain far behind. China's interior provinces lag behind the more advantaged coastal regions. Indigenous people everywhere lead far less healthy lives than do others in their respective countries, although confirmatory data are scant.

Table 1 Levels and Rates of Change in Life Expectancy, 1960-2010, by UN Region

	Life expectancy (years)			Rate of change (years per decade)	
	1960	2000	2010	1960-1999	2000-2009
World	52	66	69	3.5	2.4
China	50	72	74	5.4	2.3
India	44	62	65	4.4	3.2
Sub-Saharan Africa	42	50	53	2.3	2.7
More developed regions	70	76	78	1.6	2.0
Less developed regions	48	64	67	4.2	2.6

Source: United Nations (2009).

Much of the variation in country outcomes appears to result from the very substantial cross-country variation in the rate of diffusion of appropriate health technologies (or 'technical progress'). Countries range from having essentially no decline in infant mortality rate caused by technical progress to reductions of up to 5 percent per year (Jamison, Murphy, Sandbu and Wang, forthcoming). Measham et al. (2003) reached a similar conclusion concerning variation in IMR decline across the states of India. Cutler, Deaton and Lleras-Muney (2006) provide a complementary and extended discussion of the importance of technological diffusion for improvements in health. Consider for example the 8 million child deaths that occur currently each year. If child death rates were those seen in OECD countries, fewer than 1 million child deaths would occur each year. Conversely, if child death rates were those in OECD countries just 100 years ago, there would be 30 million child deaths a year. The key difference between now and then is not income but technical knowledge—on disease causation, interventions, and their application.

Consider the remarkable declines in infectious disease, excepting HIV, worldwide. It is difficult to overstate how much infectious disease control has improved the human condition in the last century. For comparison, the average annual death rate from all acts of war, genocide and murder in the 20th century (including noncombatants) was approximately 2 million deaths per annum. Yet reasonable estimates suggest that improved immunization saves more lives per year than would be saved by world peace. The same can be said for each of three other areas: smallpox eradication, diarrhea treatment, and malaria treatment. The development of improved environmental living conditions combined with vaccination, antimicrobial chemotherapy, and the ability to identify new microbes has been central to the more than 90% reduction in communicable disease mortality in Canada and the US (US Centres for Disease Control and

Prevention, 1996). Today more than 30 common infectious diseases are controllable with vaccines. In 1970, only 5% of the world's children under 5 were immunized against measles, tetanus, pertussis, diphtheria and polio. The Expanded Programme on Immunization has raised this to about 75% of children by 1990, saving perhaps 3 million lives a year (England et al, 2001). The clearest success in immunization is the World Health Organization (WHO)-led eradication of smallpox, which culminated in the eradication of smallpox in human populations by 1979. WHO is engaged in an ongoing effort to eradicate poliomyelitis, which is more difficult technically than smallpox eradication. Nonetheless, the effort has reduced polio cases by more than 99% to fewer than 1,000 per year.

Prior to 1950, the only major antibiotics were sulphonamides and penicillin. Subsequently, there has been remarkable growth in discovery and use of antimicrobial agents effective against bacteria, fungi, viruses, protozoa and helminths. Delivery of a combination of anti-tuberculosis drugs with direct observation (or DOTS—described below) has lowered case-fatality rates from well over 60% to 5%, and also decreased transmission. The percentage of the world's tuberculosis cases treated with DOTS has risen from 11% to about 53% (Dye et al, 2006) which points to the practical possibility of still further gains. Research into HIV/AIDS and related diseases is providing a better understanding of the internal structure of retroviruses, and is accelerating the number of antiviral agents. Sustained investment in HIV vaccine development is, very recently, beginning to bear fruit. This paper argues that investments to advance the time to availability of a vaccine would be highly attractive. Similarly, there is increasing knowledge of the modes of action of antifungal and antiparasitic agents (Weatherall et al, 2006). Large scale studies have been able to identify smoking as a major cause of tuberculosis mortality worldwide (Bates et al, 2007) but especially in India (Gajalakshmi et al,

2003). Finally, large-scale randomized trials have been increasingly used to establish widely practicable therapies, especially when modest, but important treatment benefits are sought (Peto and Baigent, 2003). Advances in computing and statistics have led to more robust mathematical models of understanding infectious disease spread (Nagelkerke et al, 2001). Finally, a new chapter is the development of molecular biology and recombinant DNA technology in the second half of the 20th Century. The benefits of DNA science to global health are as yet limited but could be extraordinary (see Weatherall et al, 2006) in DCP2.

Factors from outside the health sector also affect the pace of health improvement: education levels of populations appear quite important although the level and growth rate of income appear much less so. Of course, the importance of technical progress and diffusion should be viewed in a larger context. Expanded education improves the coverage and efficiency of disease control, as in the case of maternal education improving child health. Indeed, rapid economic growth in many parts of the world, especially in China and India, might well mean that some can buy their way into better health, but this paper argues there will be far more benefit if expanded public coffers are used on a relatively limited set of highly effective public health and clinical interventions. This point bears reiterating in a slightly different way: income growth is neither necessary nor sufficient for sustained improvements in health. Today's tools for improving health are so powerful and inexpensive that health conditions can be reasonably good even in countries with low incomes.

Reasons for remaining health inequalities thus lie only partially in poverty or income inequality: the experiences of China, Costa Rica, Cuba, Sri Lanka, and Kerala state in India, among others, conclusively show that dramatic improvements in health can occur without high

or rapidly growing incomes. The experiences of countries in Europe in the late 19th and early 20th centuries similarly show that health conditions can improve without prior or concomitant increases in income (Easterlin 1996). A recent review identified many specific examples of low-cost interventions leading to large and carefully documented health improvements (Levine and the What Works Working Group, 2007). The public sector initiated and financed virtually all of these interventions. The goal of this paper is to assist decision makers—particularly those in the public sector—to identify the highest priority low-cost interventions to rapidly improve population health and welfare health where the needs are greatest.

1.2 Remaining Challenges

Three central challenges for health policy ensue from the pace and unevenness of the progress just summarized and from the evolving nature of microbial threats to human health. ***Unequal Progress*.** The initial challenge results from continued high levels of inequality in health conditions across and within countries. Bourguignon and Morrisson (2002) have stressed that global inequalities are declining if one properly accounts for convergence across countries in health conditions, which more than compensates for income divergence. However, in far too many countries health conditions remain unacceptably—and unnecessarily—poor. This reality remains a source of grief and misery, and it is a brake on economic growth and poverty reduction. From 1990 to 2001, for example, the under-five mortality rate remained stagnant or increased in 23 countries. In another 53 countries (including China), the rate of decline in under-five mortality in this period was less than half of the 4.3 percent per year required to reach the

fourth Millennium Development Goal (MDG-4). Meeting the MDG for under-five mortality reduction by 2015 is not remotely possible for these countries.[10]

Yet the examples of many other countries, often quite poor, show that with the right policies dramatic reductions in mortality are possible. A major goal of this paper is to identify strategies for implementing interventions that are known to be highly cost-effective for dealing with the health problems of countries remaining behind—for example, treatment for diarrhea, pneumonia, TB, and malaria; immunization; and other preventive measures to reduce stillbirths and neonatal deaths. About 7.2 million of the 49 million deaths in low and middle-income countries occur in children between birth and age 5[11]. Table 2 summarizes what is known about the causes of deaths under the age of 5, and under the age of 28 days, in 2001; these proportions are unlikely to have changed substantially. Table 1 also includes an estimate on the number of stillbirths. Figure 1 illustrates that about half of all deaths under the age of 5 (including stillbirths) occur in the first 28 days, indicating the importance of addressing conditions related to this period.

[10] See Lopez, Begg and Bos (2006) for country-specific estimates of child and adult mortality rates in 1990 and 2001 that were generated in a consistent way over time and across countries.
[11] See Lozano et al (2011).

Table 2 Causes of Under-5 Mortality, Worldwide in 2001, Estimates from the GBD (in thousands)

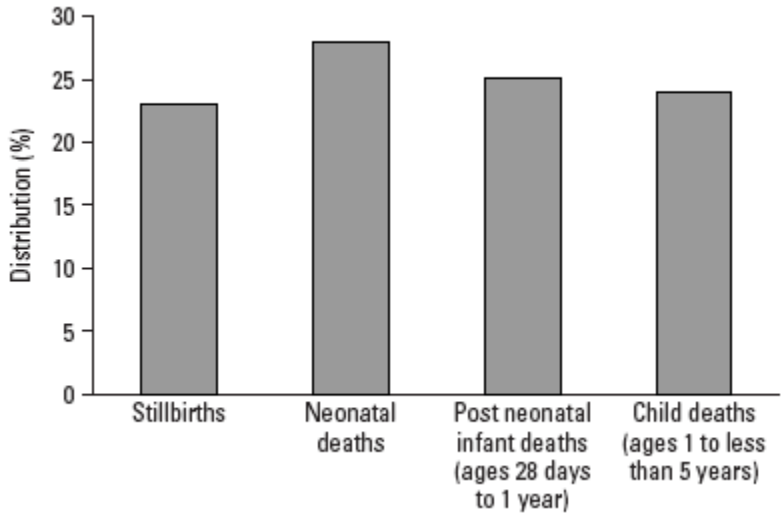
Cause	Total	Age 0 to 4	Neonatal (age 0-27days)	Stillbirths
HIV/AIDS	340	340		
Diarrheal Disease	1,600	1,600	116	
Measles	557	557		
Tetanus	187	187	187	
Malaria	1,087	1,087		
Respiratory infection (and sepsis)	1,945	1,945	1,013	
Low birth weight	1,301	1,301	1,098	
Birth asphyxia and birth trauma	739	739	739	
Congenital anomalies	439	439	321	
Injuries	310	310		
Other	5,375	2,101	446	3,274
TOTAL	13,874	10,600	3,900	3,274

Source: Mathers, Lopez and Murray (2006); Jamison et al. (2006).

Notes: 1. Of the estimated 13.9 million under-5 deaths in 2001 only 0.9% occurred in high-income countries. Thus the cause distribution of deaths in this table is essentially that of low- and middle-income countries.

2. 'Stillbirths' are defined as fetal loss in the third trimester of pregnancy. About 33% of stillbirths occur after labor has begun – so-called intrapartum stillbirths. No good estimates exist for stillbirths by cause, but some of the cause categories (e.g. birth asphyxia, birth trauma, congenital anomalies) are the same as for age 0 to 4 so part of what is categorized as 'other' in the total row will be distributed among the other existing rows when estimates are available.

Figure 1 Age Distribution of Deaths of Children under Five in Low- and Middle-Income Countries, 2001



Source: Jamison et al. (2006).

***Epidemiological Transition*.** A second challenge lies in noncommunicable disease. The next two decades will see the continuation of rising trends resulting from dramatic fertility declines (and consequent population aging) in recent decades, as well as change in patterns of risk factors. The companion CC12 paper (Jha, et. al, 2012) discusses these matters further.

The combination of an aging population paired with increases in smoking and other lifestyle changes mean that the major noncommunicable diseases—circulatory system diseases, cancers, respiratory disease and major psychiatric disorders—are fast replacing (or adding to) the traditional scourges—particularly infectious diseases and undernutrition in children. Additionally, injuries resulting from road traffic are replacing more traditional forms of injury. Responding to this epidemiological transition within sharply constrained resources is a key challenge since noncommunicable disease already accounts for two thirds of all deaths over age 5 in these countries, although nearly 22% of deaths continue to be from infection, undernutrition and maternal conditions, creating a "dual burden" that Julio Frenk and colleagues have pointed to (Bobadilla and others 1993).

***HIV/AIDS Epidemic*.** A third key challenge is the HIV/AIDS epidemic. Control efforts and successes have been very real in high and middle income countries but are not yet widespread in low-income countries. As we outline below, the HIV epidemic is best viewed as a set of diverse epidemics in regions or sub-regions. Each scenario demands understanding the reasons for HIV growth, appropriate interventions to decrease transmission to uninfected populations, and clinical care with life-prolonging drugs for those already infected. Recent data suggest that growth of HIV is slowing in large parts of Asia, Latin America and elsewhere, and that such reductions might be due to a (very uneven) increase in prevention programs. The

Copenhagen Consensus's RethinkHIV effort reviews priorities for addressing AIDS in Africa and placed accelerated work on development of a vaccine as the top priority.

2. THE ECONOMIC BENEFITS OF BETTER HEALTH

On the global scale, the dramatic health improvements during the 20th century arguably contributed as much or more to improvements in overall well-being as did the equally dramatic improvements in the availability of material goods and services. Through their substantial effects on reducing morbidity and mortality, the economic welfare returns to health investments are likely to be exceptional and positive—with only partially recognized implications for public sector resource allocation. The purpose of this section is to motivate the high values this paper (and other CC12 papers) place on mortality reduction in its cost-benefit analyses. Returns to better health go far beyond the contribution better health makes to per person income, which itself appears substantial (see Bloom, Canning, and Jamison 2004; Lopez-Casasnovas, Rivera, and Currais 2005). This section first summarizes the evidence concerning health's effect on per person income and then turns to more recent literature concerning the effect of health changes on a broader measure of economic well-being than per person income.

2.1 Health and Income

How does health influence income per person? One obvious linkage is that healthy workers are more productive than workers who are similar but not healthy. Supporting evidence for this comes from studies that link investments in health and nutrition of the young to adult wages (Strauss and Thomas 1998). Better health also raises per capita income through a number

of other channels. One involves altering decisions about expenditures and savings over the life cycle. The idea of planning for retirement occurs only when mortality rates become low enough for retirement to be a realistic prospect. Rising longevity in developing countries has opened a new incentive for the current generation to invest in physical capital and in education—an incentive that can dramatically affect national saving rates. Although this saving boom lasts for only one generation and is offset by the needs of the elderly after population aging occurs, it can substantially boost investment and economic growth rates while it lasts.

Encouraging foreign direct investment is another channel: investors shun environments in which the labor force suffers a heavy disease burden and where they may themselves be at risk. Endemic diseases can also deny humans access to land or other natural resources, as occurred in much of West Africa before the successful control of river blindness. Boosting education is yet another channel. Healthier children attend school and learn more while they are there.

Demographic channels also play an important role. Lower infant mortality initially creates a "baby-boom" cohort and leads to a subsequent reduction in the birth rates as families choose to have fewer children in the new low-mortality regime. A baby-boom cohort thereby affects the economy profoundly as its members enter the educational system, find employment, save for retirement, and finally leave the labor market. The cohorts before and after a baby boom are much smaller; hence, for a substantial transition period, this cohort creates a large labor force relative to overall population size and the potential for accelerated economic growth (Bloom and Canning, 2006).

If better health improves the productive potential of individuals, good health should accompany higher levels of national income in the long run. Although, as Acemoglu and Johnson (2007) suggest, effects or per person income may also be adversely affected by health-

related population increases. Bloom and Canning (*JPE,* forthcoming) argue that a failure to consider lags between health improvements and economic gains led Acemoglu and Johnson to underestimate the net effect of health improvements on per capita income. Countries that have high levels of health but low levels of income tend to experience relatively faster economic growth as their income adjusts. How big an overall contribution does better health make to economic growth? Evidence from cross-country growth regressions suggests the contribution is consistently substantial. Indeed, the initial health of a population has been identified as one of the most robust drivers of economic growth—among such well-established influences as the initial level of income per capita, geographic location, and institutional and economic policy environment. Bloom, Canning, and Sevilla (2004) found that one extra year of life expectancy raises GDP per person by about 4 percent in the long run. Jamison, Lau, and Wang (2005) estimated that reductions in adult mortality explain 10 to 15 percent of the economic growth that occurred from 1960 to 1990. Although attribution of causality remains equivocal in analyses like these, household level evidence also points consistently to a likely causal effect of health on income.

Health declines can precipitate downward spirals, setting off impoverishment and further ill health. For example, the effect of HIV/AIDS on per capita GDP could prove devastating in the long run. The IMF recently published a collection of important studies of the multiple mechanisms through which a major AIDS epidemic can be expected to affect national economies (Haacker 2004).

2.2 Health and Economic Welfare

Judging countries' economic performance by GDP per person fails to take sufficient account of health: a country whose citizens enjoy long and healthy lives clearly outperforms another with the same GDP per person but whose citizens suffer much illness and die sooner. Schelling (1968) initiated efforts to assign economic value to changes in mortality probability and Johannson (1995) provide and Viscusi and Aldy (2003) recent explications of the theory. Individual willingness to forgo income to work in safer environments and social willingness to pay for health-enhancing safety and environmental regulations provide measures, albeit approximate, of the value of differences in mortality rates. Many such willingness-to-pay studies have been undertaken in recent decades, and their results are typically summarized as the *value of a statistical life* (VSL).

Although the national income and product accounts include the value of inputs into health care (such as drugs and physician time), standard procedures do not incorporate information on the value of changes in longevity. In a seminal paper, Usher (1973) first brought estimates of VSL into national income accounting. He did this by generating estimates of the growth in what Becker, Philipson, and Soares (2003) later called *full income*—a concept that captures the value of changes in life expectancy by including them in an assessment of economic welfare. Estimates of changes in full income are typically generated by adding the value of changes in annual mortality rates (calculated using VSL figures) to changes in annual GDP per person. These estimates of change in full income are conservative in that they incorporate only the value of mortality changes and do not account for the total value of changes in health status.

This paper will later use a measure of 'disability-adjusted life years', or DALY, that includes disability as well as premature mortality in a way that calibrates disability weight in terms of mortality changes. Valuation of changes in mortality, it should be noted, is only one element—albeit a quantitatively important one—of potentially feasible additions to national accounts to deal with nonmarket outcomes. The U.S. National Academy of Sciences has recently proposed broad changes for the United States that would include but go beyond valuation of mortality change (Abraham and Mackie 2005). The Sarkozy Commission in France (Stiglitz, Sen and Fitoussi, 2009) reached similar conclusions. Of specific relevance to recent economic evaluations of health interventions is the economic welfare value of reductions in financial risk potentially associated either with a health intervention—typically prevention or early treatment—or with a risk-pooled way of financing it.

For many years, little further work was done on the effects of mortality change on full income although, as Viscusi and Aldy (2003) document, the number of carefully constructed estimates of VSLs increased enormously. Bourguignon and Morrisson (2002) address the long-term evolution of inequality among world citizens, starting from the premise that a "…comprehensive definition of economic well-being would consider individuals over their lifetime." Their conclusion is that rapid increases in life expectancy in poorer countries have resulted in declines in inequality (broadly defined to reflect the distributions of both mortality and income) beginning sometime after 1950, even though income inequality had continued to rise.

In another important paper, Nordhaus (2003) assessed the growth of full income per capita in the United States in the 20th century. He concluded that more than half of the growth in full income in the first half of the century—and somewhat less than half in the second half of the

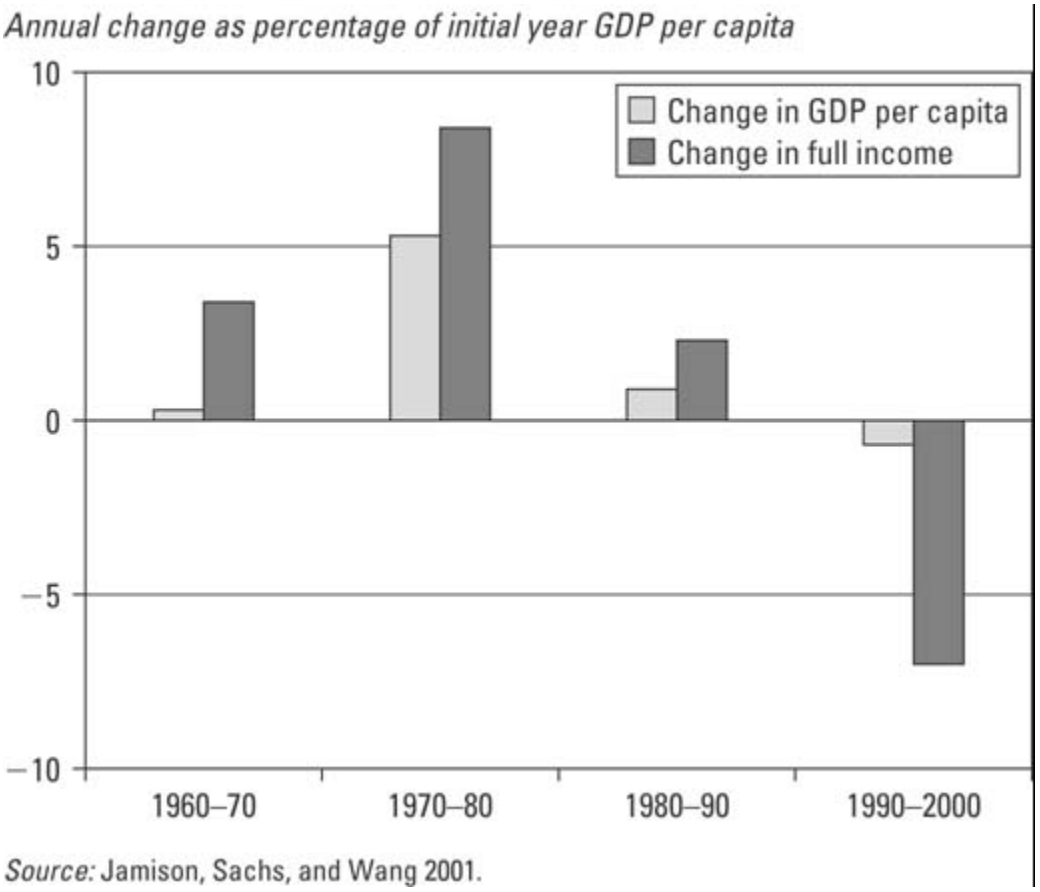
century—had resulted from mortality decline. In this period, real income in the United States increased six fold and life expectancy increased by more than 25 years.

Three lines of more recent work extend those methods to the interpretation of the economic performance of developing countries. All reach conclusions that differ substantially from analyses based on GDP alone. Two of those studies—one undertaken for the Commission on Macroeconomics and Health (CMH) of the World Health Organization (WHO) (Jamison, Sachs, and Wang 2001) and the other at the IMF (Crafts and Haacker 2004)—assessed the impact of the AIDS epidemic on full income. Both studies conclude that the AIDS epidemic in the 1990s had far more adverse economic consequences than previous estimates of effects on per person GDP growth would suggest. The benefit estimates used in this paper for successful interventions against HIV/AIDS are consistent with these findings from the CMH and IMF.

Accounting for mortality decline in Africa before the 1990s, on the other hand, leads to estimates of much more favorable overall economic performance than does the trend in GDP per person. Figure 2 shows that in Kenya, for example, full income grew more rapidly than did GDP per person before 1990 (and far more rapidly in the 1960s). After 1990 the mounting death toll from AIDS appears to have only a modest effect on GDP per person but a dramatically adverse impact on changes in full income. Becker, Philipson, and Soares (2003) confirmed and extended the earlier work of Bourguignon and Morrisson (2002) in finding strong absolute convergence in full income across countries over time, in contrast to the standard finding of continued divergence (increased inequality) of GDP per person. Finally, Jamison, Jamison, and Sachs (2003) have adapted standard cross-country growth regressions to model determinants of full income (rather than GDP per person). Like Bourguignon and Morrisson (2002) they concluded that inequalities have been decreasing.

The dramatic mortality declines of the past 150 years—and their reversal in parts of Africa by AIDS subsequent to 1990—have had major economic consequences. The effect of health on GDP is substantial. The intrinsic value of mortality changes—measured in terms of VSL—is even more substantial. What are the implications of these findings for development strategy and for benefit-cost analyses of public sector investment options? Using full income in benefit-cost analyses of investments in health (and in health-related sectors such as education, water supply and sanitation, and targeted food transfers) would markedly increase estimates of net benefits or rates of return. A major purpose of the Copenhagen Consensus process is to undertake intersectoral comparison of investment priorities by utilizing this 'full benefit' approach.

Figure 2 Changes in GDP and Full Income in Kenya, 1960-2000.



Source: Jamison, Sachs, and Wang 2001.

3. COST-BENEFIT METHODOLOGY

The basic approach to cost-benefit analysis used for most of the solutions is to start with the cost-effectiveness (CE) results from the extensive comparative analyses reported in DCP2 (Jamison et al., 2006; Laxminarayan et al. 2006). These results are expressed as the cost of buying a DALY, a summary measure involving mortality change and a valuation of disability change that can be considered to have been generated by calibration against mortality change.

Section 3.1 describers an idealized version of our approach to CE – idealized in the sense that it seeks to explicitly call attention to the value of financial protection and nonfinancial costs (e.g. use of limited system capacity). The point is to serve as a reminder in drawing conclusions of some specific important considerations that go beyond the CE ratios reported, considerations that appear in section 7 in our 'dashboard' reporting of results. Section 3.2 discusses DALYs and explicitly argues for a change in the way DALYs associated with deaths under the age of 5 are calculated. This change, which is adopted in our cost-benefit analyses, reduces the DALY cost of a typical death under age 5 by about 50% while leaving the construction of DALYs for older ages unchanged. Section 3.3 draws on Section 2 to assign, very conservatively, dollar values to DALYs for the subsequent cost-benefit assessment. Section 3.4 summarizes this paper's approach to costing.

Canning (2009) provides a valuable critique of aspects of this approach to valuing DALYs for CBA. He points to potentially lower dollar valuation of mortality reduction both in poorer countries and among the poor in a given country. This issue cuts across CC12 analyses. Our view is that $1000/DALY is a reasonable lower bound independent of the process of getting to the number.

3.1 Cost-effectiveness analysis broadly and narrowly construed

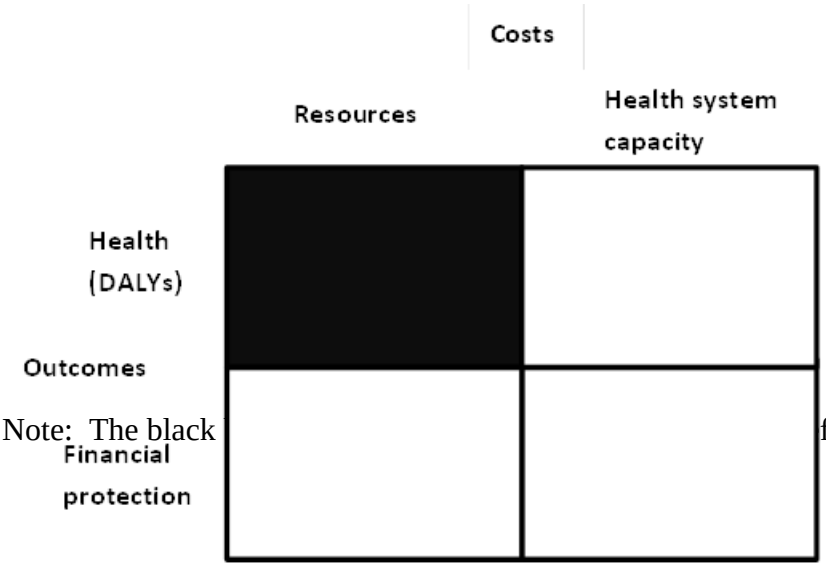
A starting point for cost-effectiveness analysis broadly construed is to observe that health systems have two objectives: (a) to improve the level and distribution of health outcomes in the population and (b) to protect individuals from financial risks that are often very substantial and that are frequent causes of poverty (WHO 1999, 2000). Financial risk results from illness-related loss of income as well as expenditures on care; the loss can be ameliorated by preventing illness or its progression, by using appropriate financial architecture for the system and by improving access to capital markets or social insurance.

We can also consider two classes of resources to be available: financial resources and health system capacity. To implement an intervention in a population, the system uses some of each resource. Just as some interventions have higher dollar costs than others, some interventions are more demanding of system capacity than others. In countries with limited health system capacity, it is clearly important to select interventions that require relatively little of such capacity. Human resource capacity constitutes a particularly important aspect of system capacity, discussed in a report of the Joint Learning Initiative (2004). Figure 3 illustrates this broadly construed vision of CE and, in its shaded region, the more narrow (standard) approach for which quantitative estimates are available. Jamison (2008) provides a more extended discussion.

Although in the very short run little tradeoff may exist between dollars and human resources or system capacity more generally, investing in the development of such capacity can help make more of that resource available in the future. Mills, et al. (2006) discuss different types of health system capacity and intervention complexity and point to the potential for

responding to low capacity by selecting interventions that are less demanding of capacity and by simplifying interventions. Mills, et al. also explore the extent to which financial resources can substitute for different aspects of system capacity (see also Gericke, et al. 2003). An important mechanism for strengthening capacity, inherent in highly outcome-oriented programs, may simply be to use it successfully—learning by doing.

Figure 3 Intervention Costs and Effects – A More General View



Note: The black ffectiveness analysis.

The literature on economic evaluation of health projects typically reports the cost per unit of achieving some measure of health outcome—quality-adjusted life years (QALYs) or DALYs or deaths averted—and at times addresses how that cost varies with the level of intervention and other factors. Pritchard (2004) provides a valuable introduction to this literature. *DCP1* reported such cost-effectiveness findings for about 70 interventions; *DCP2* does so as well, in the end providing evidence on about 315 interventions. *DCP2* authors were asked to use methods described in Jamison (2003). Cost-effectiveness calculations provide important insights into the economic attractiveness of an intervention, but other considerations—such as consequences for financial protection and demands on health system capacity—need to be borne in mind. Even if factors such as system capacity remain difficult to quantify it may be useful to include a subjective judgment, for each intervention, of the extent of its demand on system capacity. We complement our quantitative (if imprecise) estimates of B:C with subjective judgments of this type in a dashboard comparison of interventions.

3.2 Defining and Redefining DALYs

The DALY family of indicators measures the disease burden from the age of onset of a condition by combining an indicator of years of life lost (YLL) due to the condition with an indicator of years of life lost due to disability (YLD) resulting from the condition. Disability-adjusted life years (DALYs) due to a condition are the sum of the relevant YLLs and YLDs.

DALYs generate a measure of the disease burden resulting from premature mortality by integrating a potentially discounted, potentially age-weighted, disability-adjusted stream of life years from the age of incidence of the condition to infinity using a survival curve based on the

otherwise expected age of death. The formulation within the family of DALYs previously used to empirically assess the global burden of disease specifies a constant discount rate of 3 percent per year and an age- weighting function that gives low weight to a year lived in early childhood and older ages and greater weight to middle ages. The current comprehensive volume on burden of disease reports global burden of disease estimates generated with the 3% discount rate but uniform age weights (Lopez, et al., 2006a). Mathers et al. (2006) provide an extensive exploration of the uncertainty and sensitivity inherent in disease burden assessment, including the results of differing assumptions about age weighting and discount rates. [A major revision and update of the GBD is now nearing completion for publication later in 2012. Its headline reporting of results uses uniform age weighting and a zero discount rate. The practical effect is to increase markedly (and in our view implausibly) the relative importance of deaths in childhood relative to earlier publications.]

To be clear about the particular form of DALY being used, the terminology from Mathers et al. is employed. DALYs(r,K) are DALYs constructed using a discount rate of r percent per year and an amount of age weighting indexed by a parameter K. DALYs(3,1) are DALYs generated with a discount rate of 3 percent per year and with full age weighting, that is, $K = 1$. DALYs(3,0) are DALYs generated with a discount rate of 3 percent per year and with no age weighting, that is, $K = 0$. Mathers, Lopez and Murray (2006) present results concerning the burden of disease based on DALYs(3,0); Ezzati, et al. (2006) present estimates of the burden of major risk factors. This paper is based on DALYs (3,0), but slightly generalized.

A serious problem for the standard conception of DALYs concerns death near the time of birth. The DALY measure suffers from a discontinuity at this time, with a death seconds before birth counting for zero DALYs and a death seconds after counting for more than 30 (at 3%

discounting). However, while there is serious disagreement about the ethics of the beginning of life, there are very few advocates of such a discontinuous jump in moral status at the exact moment of birth.

The DALY framework can be extended to smooth out this discontinuity. This can be done using a method from Jamison et al. (2006), which introduces a concept called the 'acquisition of life potential' (ALP). The idea is that instead of instantaneously gaining full moral weight, the fetus begins acquiring it at some stage before birth, and gradually acquires full status by some stage after birth. To calculate the DALYs due to death of a fetus or infant, one multiplies the DALYs as calculated by the standard approach, by a number between zero and one which represents the current level of 'life potential'.

Operationalizing this concept involves introducing a parameter, A, that indicates the speed of ALP (see Jamison, et al., 2006 for precise definitions and assessments of the burden of disease that result.) A is constructed so that for the fastest possible speed of ALP, namely, instantaneous ALP, A = 1. A is bounded below by 0. This chapter extends the notation DALYs(r,K) in two ways. First, it explicitly indicates the level of A by extending the DALY nomenclature to DALYs(r,K,A). Thus using this nomenclature, DALYs(3,0) become DALYs(3,0,1), because the standard DALY is the special case with instantaneous ALP. Second, when stillbirths are included in the range of events to be measured in the global burden of disease, this is explicitly noted in the DALY nomenclature as DALYsSB(r,K,A). Notation around YLL is similarly extended.

Explicit modeling of ALP permits three instrumentally useful improvements to the previous formulation of DALYs:

- The ALP formulation allows, but does not require, the discontinuity in DALY loss at the time of birth to be avoided.
- The ALP formulation allows, but does not require, a positive DALY loss associated with stillbirths.
- The ratio of the DALY loss from a death at age 20, say, to that at birth is close to 1 for any reasonable set of parameter values in the previous DALY formulation. However, many people's ethical judgments would give this ratio a value substantially greater than 1. The ALP formulation allows, but does not require, these judgments.

Only a limited number of empirical studies have attempted to assess directly the views of individuals concerning deaths at different ages. In an important early study, Crawford, Salter, and Jang (1989) relate grief from a death to the concept of reproductive potential in population biology. They conclude that for several diverse human groups the relationship shows grief to be closely related to prehistoric reproductive value. An Institute of Medicine (1985) review of vaccine development priorities uses infant mortality equivalence in cost-effectiveness calculations. The committee members preparing the report collectively judged that the loss from a death at age 20 should be about two times that from an infant death. However, some preliminary trade-off studies suggest a value closer to three or four times. All three lines of evidence point to gradual rather than instantaneous ALP. What is clear, however, is that no completely defensible estimate (or even range) is currently available, and hence the numbers used in Jamison, et al. (2006) should be viewed as only suggestive. Table 5 shows the YLLs associated with deaths at different young ages for alternative formulations of the DALY, including one with their preferred value of $A = .54$. This final column reports several estimates.

(It is important to note the DALYs and YLLs for deaths above age 5 are unaffected by introduction of ALP.) *Weighting the YLLs at different ages by the relative frequency of deaths at those ages gives a* $DALY_{SB}$ *(3,0, .54) loss of 16.4 DALYs for a typical under-5 death, about half what is typically used. Our analyses use this figure.*

Table 5 Discounted YLL at Different Ages of Death for Several DALY Formulations

Age group	Representative age of death (years)	YLL(3,1)	YLL(3,0)	$YLL_{SB}(3,0,.54)$
Antepartum	–0.080	0	0	4.95
Intrapartum	–0.001	0	0	9.13
Neonatal	0.020	33.09	30.42	9.40
Infant	0.300	33.36	30.40	12.95
Postneonatal infant	0.500	33.56	30.39	15.42
Child	2.000	34.81	30.28	26.40

Source: Jamison, et al. (2006), Table 6.6.

Note: YLL(3,1), YLL(3,0), and $YLL_{SB}(3,0,1)$ assume instantaneous acquisition of life potential, ALP (A = 1). YLL(3,1) assumes full age weighting (K = 1); the other three formulations assume uniform age weights (K = 0). $YLL_{SB}(3,0,.54)$ assumes gradual acquisition of life potential (A = .54). The subscript SB refers to formulations that do not give stillbirths zero weight.

3.3 The Value of a DALY

The VSL estimates discussed in Section 2.2 yield a range of values for a statistical life—from around 100 to almost 200 times per capita income. Very approximately this can be translated to a value for a statistical life *year* in the range of 2 to 4 times per capita income. Tolley, Kenkel and Fabian (1994) provide a valuable overview of relevant estimates, including estimates of the value of preventing disability.

However, this doesn't answer the question of which income level we should use to set the value of DALY. The answer to this question is highly dependent upon what the cost-benefit calculation is being used for. For example, if Uganda is deciding whether to publicly finance a disease control programme, the money raised for this would come from the Ugandan people. Their nominal GNI per capita is about $500, so the above method would suggest that the Ugandans would value a DALY as much as a sum of money between $1000 and $2000. Thus it would be counterproductive for their government to spend more than $2000 to provide a DALY. In this usage case, where a country is spending its own money to help its own citizens, we need to use each country's GNI to determine their dollar value of a DALY and hence their BCRs. It is irrelevant to the Ugandans that the Nigerians have a GNI per capita of approximately $1180 and would thus value a DALY at more than twice as many dollars.

In contrast, if we are trying to produce a global prioritization, there are strong ethical reasons for using a single dollar value for DALYs (or VSLs) no matter which country they occur in. Otherwise we would be failing to value all people equally and would end up grossly neglecting death and disability in poorer countries. Since the interventions in this chapter affect people in relatively poor countries, this effect is limited but could still be as much as a factor of

10 or 20. However, if we wanted to compare these interventions with interventions that affected people in high-income countries, then the effect could rise to a factor of 100, with a DALY being valued at $100,000 to $200,000 in the US. While there are no health interventions for US citizens discussed here, the problem could come up between chapters for any type of benefit for members of high- or middle-income countries calculated from their willingness to pay.

For the reasons above, there cannot be a single dollar value that we can place on a DALY or a VSL to take account of the different ways in which people might wish to use it. The best compromise that we have been able to find is to use a single figure based on the average income in our target countries. The emphasis in this paper is on low-income countries defined by the World Bank for 2001 as countries with per capita incomes of less than $1005 (exchange rate). The World Bank's estimate of the average income of people living in low-income countries is $509 per year (World Bank, 2011, Table 1.1). Choosing a value for a statistical life year near the low end of the range (a little above 2) would give a convenient value of $1,000, which is what this paper uses in its main calculations as the value of a DALY. (Note that for the reasons discussed in Section 3.2 the DALY loss from a death under age 5—and hence the benefit from preventing it—is about half that used in standard DALYs.)

Note that health programmes in poor countries should adjust this number according to their own national incomes, as mentioned in the sensitivity analysis in Appendix A. Furthermore, comparisons between this chapter and any cost-benefit analysis where willingness to pay has been calculated based on the preferences of people in a richer country will need to scale these ratios up accordingly. For example, while our recommended TB programme has an indicative benefit-cost ratio of 20:1, the benefit-cost ratio of the programme should be thought of as 2000:1

if it were being compared to interventions that benefitted people in the US and used American willingness to pay estimates.

We explore the sensitivity of our results to these effects in Appendix A, as well as considering a DALY value of $5000 for low income countries and the standard DALYs (DALYs (3,0)) for child deaths.

3.4 The Cost of a DALY

The cost of buying a DALY with different interventions was calculated, in DCP2, by combining 'typical' prices for a geographical region (Mulligan, et al. 2003) with input quantities estimated from clinical and public health experience and case studies in the literature. Because solutions being considered usually involve substantial increments from the status quo, long-term average costs were used. For internationally traded inputs prices were the same for all regions.[12] For local costs regional estimates were used. Intervention costs, therefore, are *not* expressed in PPP dollars. The reason for this is that local costs present decision-makers with the appropriate numbers for budgeting and for comparing interventions in the context where they are working. Regional costs are taken to be a better approximation of these local costs than global costs would be. On this point the methods of this paper differ from those of CC04 (Mills and Shilcutt, 2004).

[12] Because of tiered pricing, on-patent drugs were *not* considered to be internationally traded.

4. CHILD HEALTH

A small number of conditions account for most of the large differences in health between the poor and the not so poor. For example, less than 1 percent of all deaths from AIDS, TB, and malaria occur in the high-income countries. Available technical options—exemplified by but going well beyond immunization—can address most of the conditions that affect children, and can do so with great efficacy and at modest cost. That short list of conditions, including undernutrition, relates directly to achieving the MDGs for health. The section begins by discussing intervention to address under-5 mortality. It then turns to the problem of the world's most prevalent infections, intestinal worm infections, and the relatively straightforward approach to dealing with those in schoolchildren. The final subsection discusses delivery and includes two of our solutions for CC12: pricing mechanisms to facilitate uptake of appropriate antimalarials and the essential surgical platform.

4.1 Under-5 Health Problems and Intervention Priorities

The Millennium Development Goal for under-5 mortality (MDG-4) (reducing its level in 2015 by two-thirds relative to what it was in 1990) is highly ambitious. Yet its implication of an average 4.3 percent per year decline is well within recent experience. In the first half of the MDG period (1990–2002), 46 countries achieved rates of decline in under-five mortality greater than 4.3 percent per year (Lopez, Begg and Bos, 2006).

Basic knowledge about the power and the cost-effectiveness of interventions to address maternal and child health has been available for many decades. DCP2's work makes four

important and relatively new points. First, major declines in childhood mortality could well be accelerated with expanded case-management of acutely ill children and with the addition of several new antigens to routine vaccination. These include *Haemophilus influenza* type b (Hib) and *Streptococcus pneumonia* which are common causes of childhood pneumonia; hepatitis B which protects against liver cancer; and newer rotavirus and shigella vacinnes against diarrhea (England et al, 2001). The Global Alliance for Vaccines and Immunization (GAVI) estimates that the addition of Hib and pneumococcal vaccines to vaccination programs could save 800,000 lives a year by 2010. Further GAVI estimates suggest that rotavirus and shigella vaccines might save 600,000 lives a year by 2010.

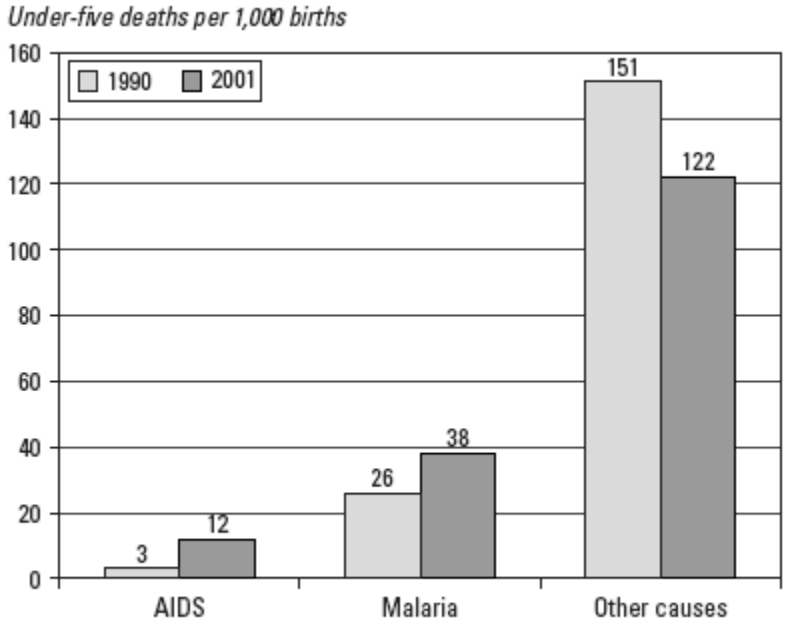
Second, half of under-five deaths occur at ages less than 28 days (Figure 1), when the substantial but usually neglected problem of stillbirth is considered. DCP2 identifies some highly cost-effective approaches to intervention against stillbirth and neonatal death (Lawn et al., 2006). These include increased reliance on delivery in facilities with surgical capacity to deal with complex obstetric emergencies, which are life-threatening both for mother and for child.

Third, there is a rapid spread of resistance of the malaria parasite to chloroquine and to sulfadoxine-pyrimethamine (SP). These inexpensive, highly effective, widely available drugs provided an important partial check on the high levels of malaria deaths in Africa, which are concentrated particularly in children. Their loss is leading to a rise in malaria mortality and morbidity that could be substantial. Figure 4 illustrates increases in malaria death rates and decreases in death rates from other causes except AIDS in under-five children in Sub-Saharan Africa in the period from 1990 to 2001. This death rate increase results in hundreds of thousands of deaths more than would otherwise have occurred. [With malaria, however, there is increasing evidence that widespread use of bednets and better treatment is partially reversing the adverse

trend prior to 2011. See WHO (2011).] The design of instruments for financing a rapid transition to effective new treatments—artemisinin combination therapies (ACTs)—is a high priority. Kenneth Arrow chaired a committee of the U.S. Institute of Medicine to design appropriate financial instruments (Institute of Medicine, 2004; Arrow, Gelband, and Jamison 2005). This resulted in creation of the Affordable Medicines Facility-malaria (AMFm), which would reduce the relative prices which public or private sector providers face for ACTs rather than increasing their budgets for purchasing them. This effort is now underway and early results indicate that the mechanism has been successful in lowering the price of ACTs in eight pilot countries. Fourth, although education interventions are considered in a separate paper for CC12 (Orazem, 2012), it is worth noting here that improvements in the quality of basic education can plausibly have benefit to cost ratios as high as for many health interventions – even if no benefits of education other than mortality reduction are included. In a recent paper, Jamison, Jamison and Hanushek (2006) estimate that the effect of a one standard deviation improvement in quality[13] would increase the annual rate of decline of infant mortality by about 0.6% leading, after 20 years, to something over a 10% reduction in IMR relative to what it would otherwise have been. They estimate that this effect could be achieved for on the order of 10% of the cost of a year of schooling, which is likely to be less than $100 per student per year in a low-income country.

[13] As measured by scores on internationally standardized achievement tests, particularly those in mathematics.

Figure 4 Under-Five Deaths from AIDS, Malaria, and Other Causes, per Thousand Births, 1990 and 2001, Sub-Saharan Africa



Source: Lopez, Begg, and Bos 2006, table 2.4.

Note: A major update of the GBD will be published in 2012, covering the period 1990 to 2012, and it may show (recent) improvements in malaria mortality.

If the total fertility rate is 3 and the base level of IMR is 70 per 1000 then education quality improvement is likely to result in a cost per (undiscounted) child death averted of around $1000.

Assuming (as this paper does) a low DALY loss per child death of about 16 and the value of a DALY in low income countries to be $1000 then the B:C ratio will be about 13. Discounting the benefits at 5% would give a B:C of 4, again ignoring any other benefits from the education. Increasing the value of a DALY from $1000 to $5000 would increase the B:C ratio to 20 even with 5% discounting. In our next subsection we turn to a mechanism through which health intervention - deworming – can contribute to increasing both the quantity and quality of education with benefits through the mechanism reviewed here, on the next generation.

In addition to the above, other intervention priorities for addressing under-five mortality are for the most part familiar:

- Exclusive early breastfeeding, which has increased widely in all parts of the world over the last few years.
- Expand immunization coverage of the current set of antigens in the Expanded Program on Immunization (EPI), as well as addition HiB, hepatitis B, rotavirus and streptococcus.
- Expand the use of the simple and low cost but highly effective treatments for diarrhea and child pneumonia through integrated management of childhood illness or other mechanisms.
- Prevent transmission of malaria by expanding coverage of insecticide-treated bednets, by expanding use of intermittent preventive treatment for pregnant women; and by use of indoor residual spraying with DDT.
- Enable use of effective antimalarial medication, and prevent the development of resistance to it by subsidizing its price to make it affordable and to crowd out counterfeits and monotherapies that will speed resistance. The Affordable Medicines Facility, malaria (AMFm) has been successful in doing this in its initial year. Its continuation and

expansion is one of the 5 priorities this paper recommends, in part because it addresses the externality associated with monotherapy induced antibiotic resistance.

- Ensure widespread distribution of key micronutrients, most notably Vitamin A, Zinc, and iron. (See the CC12 paper on nutrition, Hoddinott et al, 2012.)
- Expand the use of antiretrovirals and breast feeding substitutes to prevent mother-to-child transmission of HIV.

4.2 Worm Infections in School Age Children

In addition to interventions to reduce under-five mortality, one other priority is increasingly clear. The world's most prevalent infections are intestinal helminth (worm) infections, and children of all ages are among the most heavily affected. Hotez, et al. (2006) discuss these infections, which a low-cost drug (albendazole), taken every six months to a year, can control effectively. Bundy, et al. (2006)'s discussion of school health services points to both the importance to children's school progress of taking albendazole where needed and the potential efficacy of school health programs as a vehicle for delivery. Canning (2009) emphasized that standard health-related CEAs fail to capture the importance (and feasibility) of deworming and the CC08 overall ranking for deworming was number 6 out of 30 (Bhagwati, et al, 2009). In the long run, improved sanitation and water supplies will prevent transmission of worm infections. Use of albendazole is only an interim solution until development-driven sanitation improvements take over, but it is one that may be required for decades if the experience of the currently high-income countries is relevant.

Worms remain a neglected infection despite the high prevalence and the low-cost treatment (Bundy et. al 2006). Regions such as Sub-Saharan Africa, Southeast Asia and parts of Latin America are disproportionally affected by worms due to poor and unsanitary living conditions and personal hygiene (Hall and Horton, 2009). Human behavior, climate and overcrowding can all contribute to the survival and transmission of worms. From complications with digestion to difficulty absorbing nutrients, worms can be detrimental to a person's overall wellbeing, including productivity, appetite, fitness, and growth (Stephenson, 1987; Bundy et al, 2004). Children are at greater risk of infection than adults and will suffer more severe, lifelong complications if worms are left untreated. Children who do experience worm infection often live in poor communities and need a sustainable treatment plan to remedy any loss in education, nutrition and intellectual development they may experience. Behavioral patterns of children put them at greater risk of serious infection than other age groups.

Currently there is much literature suggesting deworming programs are extremely cost-effective. According to Deworm the World, a joint initiative launched in 2007 by the World Economic Forum, deworming programs are one of the most cost-effective health interventions in the world (Deworm the World, 2009). It is helpful in analyzing the educational consequences of deworming programs to consider more explicitly than is typical for education administrators the relation between system capacity and system utilization. The number of student places needed to serve a catchment area is simply the population size in the relevant age cohort, here ages 5-14, times the percentage of that cohort that would ideally be in school (for this age group it would be 100%). Each student place requires (given local policies on class size) a certain amount of physical plant, teacher availability, and so forth; the level of those resources actually available determines the number of student places installed. Enrolment will typically be less, perhaps

substantially less, than the number of places installed due to dropouts and repetitions leaving upper-grade classrooms only partially filled; similarly, student absences on any given day will leave classrooms only partially utilized. The ratio of utilization to capacity provides, we suggest, the appropriate measure of the *quantitative* efficiency of a school system. (The concept of *qualitative* efficiency, which relates the rate of learning to the expenditure per student-year of actual attendance, is more frequently discussed in the literature.) Miguel and Kremer (2004) find the major effect of deworming in Kenya to be on quantitative efficiency: treated children ended up acquiring 0.15 additional years of school, at only the cost of deworming because capacity limits had not been met. Orazem, Glewwe, and Patrinos (2009) stress the importance of explicit attention to these limits which suggest corresponding limits on extent of potential impact of deworming absent complementary investments in educational infrastructure.

The preceding discussion has provided a structure for deworming in the context of interventions to affect educational outcomes. The examples developed by Jamison and Leslie (1990), and Horton and Hall (2009) and the Kenya work of Miguel and Kremer (2004) all point to the potential for *highly* attractive cost-effectiveness or cost-benefit ratios from deworming's effect through school. In the Copenhagen Consensus 2008's assessment of educational priorities deworming ranked high (Orazem, Glewwe, and Patrinos, 2009) as it also did in the context of assessing nutritional priorities (Horton, Alderman, and Rivera, 2009). And, as previously noted, the 2008 Copenhagen Consensus Expert Panel of distinguished economists (Bhagwati et al, 2009) ranked school-based deworming number 6 in its assessment of 30 development priorities.

When turning to the health dimension of outcomes and cost-effectiveness there has been substantial recent controversy. GiveWell in its review of DCP2's estimates of cost per DALY found (in collaboration with the DCP2 authors) important errors that suggest (from a health

perspective) that deworming may be far less cost-effective than thought. A major problem was an error in WHO's published disability weights for helminthic infection[14].

Two related issues arise in trying to express health loss from worm infections in an aggregate measure like the DALY. The first is that the DALY loss from these infections is very little in mortality (years of life lost or YLLs) and substantially in disability (YLDs). The effective disability weights are small but multiplied by an enormous number of infections. Whether the product is large or small depends entirely on the disability weights and we would assert that *estimating these small disability weights with any accuracy is far beyond the state of the art.* A second, related problem is that the distribution of intensity of worm infections is highly 'over dispersed,' i.e. only a few people harbor most worms (Bundy, et al, 2004; Hall and Horton, 2009). Defining who is sick, and how sick, becomes rather arbitrary even though the definitions may be quite clear. We suggest discussion of health related cost-effectiveness for deworming not use DALY's and focus instead on costs per 'real' outcome: person treated; infected person treated; 'diseased' person treated (at greater than or equal to 10 worms, etc.). Hall and Horton (2009) implementation paper for CC08 provides an excellent example.

4.3 Delivering Reproductive and Child Health Interventions

[14] See http://blog.givewell.org/2011/09/29/errors-in-dcp2-cost-effectiveness-estimate-for-deworming/

The list of potential interventions is far from exhaustive and different regions, countries, and communities will face different mixes of the problems these interventions address. However, there can be little dispute that any short list of intervention priorities for under-five mortality in low- and middle-income countries would include many on the list in the preceding sections. Why not, then, simply put money into scaling up these known interventions to a satisfactory level? In this section we first discuss constraints to scaling up and approaches to overcoming them. We next discuss a specific financial mechanism – the AMFm – in detail and conclude that its continuation and expansion is a high priority. Finally we discuss the neglected priority often accorded to the platform of essential surgery. Much of what surgical intervention addresses deals with complicated delivery, contraception (vasectomy, tubal ligation and sub dermal hormones) and injury.

Overcoming implementation constraints. To greatly oversimplify—and these issues are discussed more substantially in Mills et al. (2006)—two schools of thought exist. One line of thinking—often ascribed to macroeconomist Jeffrey Sachs and his work as chair of the WHO CMH—concludes that more money and focused effort *are* the solutions. Although acknowledging dual constraints—of money and of health system capacity—Sachs and his colleagues (WHO CMH 2001; Sachs 2005) contend that money can buy (or develop, or both) relevant system capacity even over a period as short as five years. Major gains are affordable and health system capacity constraints can be overcome. Immunization provides an example of where, even in the short term, money can substitute for system capacity. Adding newer antigens to the immunization schedule is costly (although still cost effective). In some environments, however, it proves less demanding of system capacity than expanding coverage does. Money

can be effectively spent by adding antigens at the same time as investing in the capacity to extend coverage.

A second school of thought acknowledges the need for more money but asserts that health system capacity is often a binding short- to medium-term constraint on substantial scaling up of interventions. Van der Gaag (2004) emphasized this point in his critique of an earlier Copenhagen Consensus paper on health. Critical priorities are, therefore, system reform and strengthening while ensuring that such reforms focus clearly on achieving improved health outcomes and financial protection.

This paper's perspective is closer to that of Sachs than of Van der Gaag while emphasizing the need (in Section 3.1) to be explicit about intervention costs that are nonfinancial. This points both to the need for considering how to relax these constraints and to selecting interventions in part on the extent to which they are less demanding of nonfinancial inputs. Frenk, Sepulveda and others have described a "diagonal" approach being used in Mexico where systems are strengthened while focusing on specific disease outcomes. Experience suggests that while such an approach demands considerable management, it is highly effective.

Against a backdrop of low immunization coverage in Africa, Malawi, one of the poorest countries in the world, has succeeded in boosting immunization coverage against measles from only 50% in 1980 to almost 90% today. Malawi undertook a program to raise routine measles immunizations including campaigns to catch children missed out by routine efforts. As a result, the number of reported cases and deaths has fallen dramatically. During 1999, only two laboratory-confirmed cases were reported. And, for the first time ever, no measles deaths. Yet only two years earlier, almost 7000 measles cases were reported and 267 deaths (both of which are likely to be undercounts). This was achieved despite one in five of the population not having

access to health services, and less than 50% have access to safe water, and only 3% have access to adequate sanitation. (Jha and Mills, 2002).

Mills, et al. (2006), as indicated, discussed these issues further in the context of all the problems facing a health system. From an individual country's perspective, however, if financial resources are available, the question is very much an empirical one: to what extent can those resources be effectively deployed in buying interventions, in buying out of prevailing system constraints, and in investing in relevant system capacity for the future? Accumulating experience suggests that to be successful, these choices will involve sustained funding to achieve specific outcomes (Jha et al, 2002; Crogan, 2006).

The Affordable Medicines Facility malaria (AMFm). Innovations in financing and delivery have been a key feature of global health investments during the past decade. The number of privately initiated, publicly funded innovative financing mechanisms includes GAVI (for vaccines), Global Fund for AIDS, TB and Malaria (for antiretrovirals, TB drugs and diagnostics, bednets and drugs for malaria), Advance Market Commitments (for pneumococcal and other vaccines) and more recently the Affordable Medicines Facility for malaria (AMFm). AMFm was created in 2010 as a separate arm of the Global Fund to implement the pilot phase of a high-level subsidy for artemisinin-based combinations (ACTs) in eight countries in sub-Saharan Africa. The original idea of AMFm was mooted by the Institute of Medicine committee as a response to the problem of growing artemisinin monotherapy use in retail shops where treatment for malaria is most frequently obtained. And artemisinin monotherapy could increase the likelihood of parasite resistance to artemisinins, the last major class of compounds that are still effective against malaria parasites. ACTs were available in some public sector facilities

through donor financing and in the private sector at a cost of between $8 and $12, which is out reach for all but the wealthiest section of the population in malaria-endemic countries. Artemisinin monotherapies, and monotherapies of the drugs used to protect artemisinin in ACTs, were typically available at far lower prices with the obvious behavioral consequences.

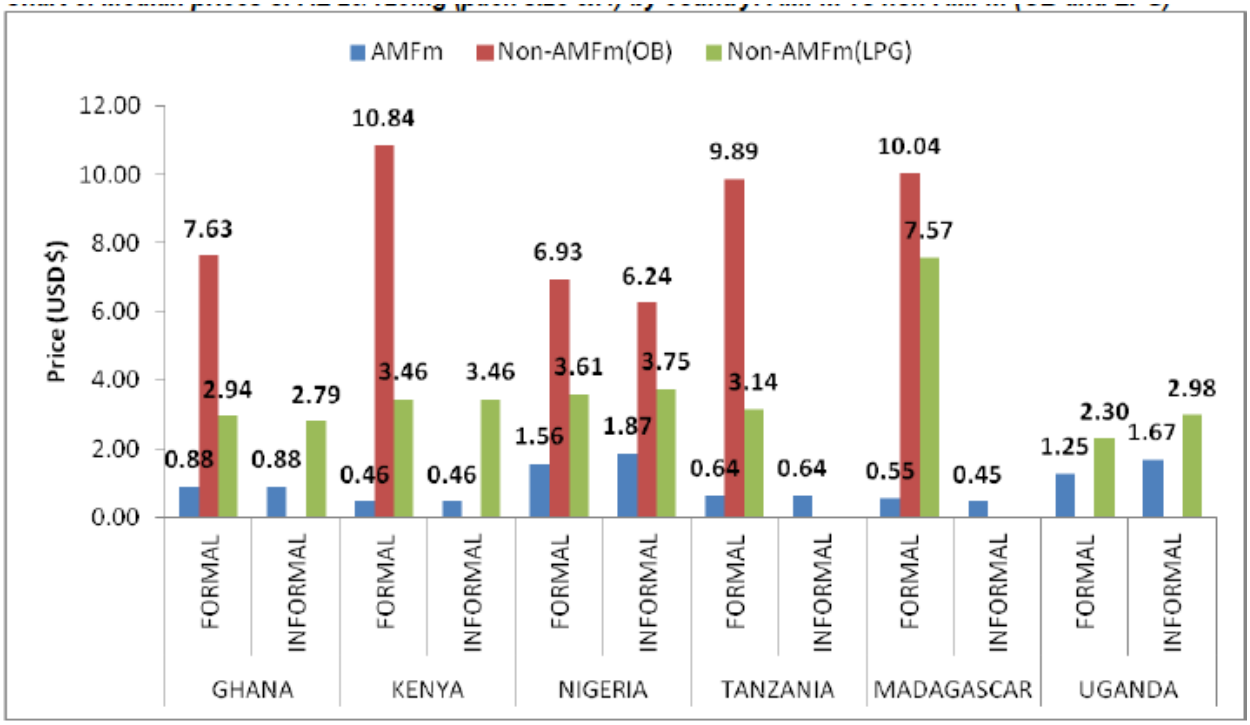
A high level subsidy for quality ACTs, it was argued, would crowd out monotherapies from the informal private sector, increase access to these drugs in both public and private sectors, lower ACT prices by ensuring stable and high demand, and lower incentives for sales of counterfeit and expired artemisinin drugs. Since the cost of delivering the drugs would be borne largely by private sector supply chains, the donor cost of the subsidy would be restricted to the difference between the unsubsidized wholesaler price and the subsidized price.

Early cost-effectiveness estimates based on sophisticated mathematical models of malaria transmission and resistance indicated that a child death could be averted at roughly $1000 (Laxminarayan, Over, Smith, Health Affairs 2006). Similar estimates are obtained through back-of-the-envelope calculations. One million USD spent on a subsidy would expand access to 300,000 more children with malaria (based on 67% of AMFm ACTs being pediatric formulations), treat 20,000 severe malaria cases and avert roughly 1000 child deaths. This calculation does not include the benefits associated with averted resistance because of crowding out artemisinin monotherapy, the benefits of lower counterfeit drugs use, or of price reductions because of stabilized demand for ACTs. According to a recent model based study, the discounted externality benefits of resistance reduction including (a) the reduction in malaria transmission from infected to susceptible individuals due to increased overall drug treatment and (b) the increase in average drug effectiveness which benefits treated patients themselves, as well as

reducing infection transmission from them to other individuals; and less the discounted gross distortionary cost of the subsidy, is about 6:1 (Laxminarayan et al, 2010).

Early evidence from the AMFm pilot indicates that the goal of lowering ACT prices relative to other drugs in the retail sector has been achieved in nearly all AMFm countries (see Figure 5). The ratio of the price of a full course of AMFm subsidized ACTs to the price of a full course of the lowest priced generic ranges from 1:2 in Nigeria and Uganda to 1:14 in Madagascar. The ratios are even more stark when the price of AMFm drugs is compared to the price of non-AMFm branded drugs, and range from 1:3 in Nigeria to 1:23 in the Kenyan formal sector. A full independent evaluation of the AMFm pilot has been commissioned by the Global Fund board and is expected in September 2012. This is expected to shed more light on the utility of this novel market-based mechanism in drug delivery, and inform a future course of action once the large scale pilot funding runs out in December 2012. One of our CC12 solutions is that continued funding for AMFm claims high priority.

Figure 5: Median Prices of AL 20/120 mg (pack size 6x4) by country: AMFm vs non AMFm (OB- Other Brands and LPG – Lowest Priced Generic)



Essential Surgery. Almost one in ten pregnancies is developing countries result in deliveries with major complications – heavy bleeding, torn tissues or obstruction to the child's passage that leads to days of extreme pain and often death for the mother and child. Dealing with these problems usually requires surgical intervention (although not necessarily by a board-certified surgeon or obstetrician.) A range of correctable problems of the very young also require surgical intervention and the global community has advanced 'safe motherhood' initiatives to strengthen national capacity to deal with these problems. The same skill sets – surgery, anesthesia, nursing - that can respond to complications of pregnancy can also respond to a range of other problems, most prominently trauma including burns but also a range of abdominal problems and suppurative infections common in developing countries. (See Mock et al, (2009) for a discussion of priority areas for essential surgery.)

Debas et al (2006) in DCP2 decided to undertake CEA of a modest district hospital (100-bed) with some degree of surgical capacity rather than to look at the cost-effectiveness just of obstetric or other specific surgical interventions. The reasoning is that investment in expanding capacity or improving quality are at this *platform* level, a platform that responds to multiple and diverse problems. For undertaking CEA they assessed all the costs of operating the district hospital surgical platform for a year. For effectiveness they looked, in different epidemiological environments, at the annual mix of admissions and at the consequences (using best judgment to apportion part of the consequence to surgical intervention.) An early example of this platform analysis comes from Bangladesh where low costs and substantial numbers of (probably) obstetric deaths averted led to highly favorable cost-effectiveness estimates. (McCord and Chowdhury, 2003). Debas, et al's best estimates of cost per DALY for what we might call essential surgery

range across geographical regions from $40-100, with their high estimates at about twice their best estimates.

Why might such surgery appear so cost-effective? Like the drugs for malaria, TB, AIDS pneumonia and other infectious killers, a one or two hour surgical procedure can change outcomes decisively: from death to a 4-week recovery or from being seriously crippled for life to having a mild limp. Very basic surgery can achieve these outcome changes at modest cost.

5. HIV/AIDS

For dozens of countries around the world—including several of the most populous—the AIDS epidemic threatens every aspect of development. No other threat comes close, with the possible exceptions of use of nuclear weapons in densely populated areas or a devastating global pandemic similar to the 1917–18 influenza episode. Most governments of affected low- and middle-income countries and most providers of development assistance have only recently begun to respond more than minimally. Creation of the Global Fund to Fight AIDS, Tuberculosis, and Malaria can be viewed as an attempt of the world's top political leaders to improve on the records of existing institutions. The Global Fund's initial years have seen substantial success, but that success is being undermined by sharp constraints on resource availability, as had been foreseen by Bezanson (2005).

Thirty years have passed since the recognition of the infectious disease now named acquired immune deficiency syndrome (AIDS). In that relatively short time AIDS has killed over 30 million individuals, and an additional 33.3 million people are now living with the infection. Africa shoulders the burden of the epidemic: UNAIDS estimates that in 2009 1.3 million people died from AIDS in Africa, 22.5 million were living with the infection, and a further 1.5 million

acquired the infection during the year. Even though prevention and treatment programs are expanding, the epidemic is holding its ground. Only 2 out of every 5 people requiring antiretroviral therapy currently have access to treatment – and this number is threatened by financial pressures. Though universal access to treatment is a morally compelling goal, the high costs associated with treatment argue for a strategy that emphasizes prevention (See UNAIDS et al, 2010; Hecht et al, 2010).

In contrast to the initially slow programmatic movement of most national leaders and international institutions, the research and development community—public and private—has made rapid progress in developing tools to control the HIV/AIDS epidemic. Sensitive, specific, and inexpensive diagnostics are available; means of prevention have been developed and tested; modes of transmission are well understood; and increasingly powerful drugs for controlling viral load allow radical slowing of disease progression. Tools for dealing with HIV/AIDS are thus available: Bertozzi and Padian (2006) emphasized that a number of countries have shown by example that those tools can be put to effective use. Most of the high-income countries have done so, and Brazil, Mexico and Thailand provide examples of upper-middle-income countries that have forestalled potentially serious epidemics (del Rio and Sepúlveda 2002).

This section first discusses behavioral prevention and medical then vaccine development. It closes with a discussion of antiretroviral therapy. It draws importantly on papers prepared for the 2011 Copenhagen Consensus effort Rethink AIDS.

5.1 Prevention of HIV Transmission

The reasons for the variations in prevalence between countries are not entirely clear despite substantial research. It is now established that high levels of male circumcision protect against HIV transmission at the population and individual level (Abdool Karim, 2007). High levels of genital ulcer disease and low levels of male circumcision may help to explain the high levels of HIV infection seen in southern and eastern Africa. However, conditions rife for rapid growth exist in many places. These conditions include high levels of paid sex and partner change, common sexually transmitted infections (STIs), low condom use rates, male mobility and migration, and low rates of male circumcision. These points suggest the opportunities for preventive intervention.

The key challenge for HIV/AIDS policy is to prevent HIV transmission. In the absence of a vaccine, several interventions are of key importance. For the Copenhagen Consensus effort Rethink HIV, Bollinger (2012) reviews benefits and costs of options for presenting nonsexual transmission and Behrman and Kohler (2010) assess sexual transmission. The most clearly effective preventive interventions against HIV are those targeting groups that—because of high rates of partner change, increased susceptibility to infection, or both—are highly vulnerable. Peer interventions among sex workers teach them high levels of condom use, control of STIs, and client negotiation skills that appear highly effective. Sex workers and their clients represent an important vulnerable group who are central to the spread of HIV in most populations, including in Africa and vulnerable groups might even be important in early as well as late stages of the epidemic (Chen et al, 2007). In some contexts fewer than one sex worker would need to be covered in a program for one year to prevent one infection (Jha et al, 2001).

A few countries in Asia with conditions for rapid growth in HIV infections acted early by scaling up vulnerable group interventions. Their common principles were to work with the commercial sex industry, map where it occurs, aim for high coverage, and base action on solid epidemiological information. The results are impressive. Thailand is the most famous example, where HIV peaked in the early 1990s and has stayed at below 2% seroprevalence since. Less known are Mexico (del Rio and Sepúlveda, 2002) and Cambodia, which copied the Thai "100% condom" program in commercial sex in 1997 in one state, and has shown impressive declines in HIV. More recent evidence from the 4 southern states of India suggest that new HIV infections might have dropped by 30%, probably due to change in sex work (either the proportion using condoms or men going less often to sex work; Kumar et al, 2006).

Other interventions that complement vulnerable group interventions are effective. Despite controversy about the evidence, the best judgment is that STIs remain important as risk markers and risk factors for HIV spread. STI treatment for vulnerable and general populations is probably effective for HIV control. Voluntary counseling and testing has led to some reduction in unsafe behavior in some studies, though the duration of the change is not clear. However, such testing is not necessarily a cost-effective form of prevention in all or even most settings, especially where prevalence is low. Voluntary testing is, however, a necessary prerequisite to some forms of treatment.

Although the transmission of HIV from mother to child is not of great epidemiological importance, since the infected children are very unlikely to transmit the disease, it is a mode of transmission that can be blocked. Short courses of single anti-retrovirals can halve transmission risk from about 40% to 20%. To be fully effective, replacement feeding is also required, given

that breast milk is a source of transmission. Finally, needle exchange programmes and blood safety programmes can reduce these less common modes of transmission.

More broadly, prevention efforts appear to work best when there is national leadership and simultaneous, sustained investment in multiple approaches to prevention, including efforts to reduce stigmatization of vulnerable groups. Increasing the availability of condoms for the wider population can be enabling of more focused action. For example, the proportion of Senegalese women easily able to procure condoms rose from below 30% to 80% between 1992 and 1997. Focused information campaigns aimed at building public support and awareness are also seen to be important, although these are not likely to change behavior by themselves reinforcing the message of simultaneous use of multiple interventions.

In those sub-Saharan countries with generalized epidemics that have spread far beyond vulnerable groups, the national approach is a necessity. The reasons for the sharp decline in HIV prevalence in Uganda, from about 20% in 1990 to 10% in 1999, are widely debated. It may be due, at least in part, to a broad-based prevention strategy addressed at the population as a whole, or due simply to the fact that high death rates among the most susceptible helped the epidemic to decline (James 2005). The replicability of the Ugandan experience to lower-prevalence settings is not established.

Bertozzi, Padian et al. (2006) point out that even by 2003 fewer than one in five people at high risk of infection had access to the most basic preventive services. In much of the world, little has been spent on prevention, and little has been achieved. In addition, fundamentalist factions in both national governments and the development assistance community may be partially responsible for discouraging condom use in some countries and in stigmatizing and alienating commercial sex workers who are particular priorities for prevention programs.

Despite those problems, the potential for prevention is very real, and a number of successful countries have shown the possibility of using that potential well. Piot, et al. (2008) summarized experience to date by observing that while evaluations of single interventions have often failed to find an impact the countries that have mounted major programs of "combination prevention" have often achieved substantial success. The ingredients in the combination cocktail will vary by location but Piot argues that there is now reasonable evidence for its general success. Combination prevention was on the solution list for CC08.

5.2 AIDS Vaccine Development

An AIDS vaccine[15] is the ultimate preventative tool—vaccination would provide a manageable and affordable way to confer protection against HIV infection. When fully developed and licensed, an AIDS vaccine could have a powerful and immediate impact; the International AIDS Vaccine Initiative (IAVI) estimates that an AIDS vaccine of 50% efficacy given to just 30% of the population could reduce the number of new infections in the developing world by 24% in 15 years (IAVI, 2009). Yet AIDS vaccine development is proving to be enormously expensive. Is the perhaps $15-20 billion of additional resources that it may cost the world to develop an AIDS vaccine worth it?

One of the papers in the RethinkHIV project addressed the potential returns to expanding the technological base through development, manufacture and utilization of a vaccine to prevent HIV infection (Hecht and Jamison, 2011). That paper did not argue for investment in vaccine development at the expense of ongoing HIV prevention or treatment interventions. Rather, it

[15] We use the term 'AIDS vaccine' to denote the probable set of vaccines that could emerge from ongoing development efforts. Hypothetical values of vaccine cost and efficacy in this paper are for the best (mix) to emerge over time, and in a more extended assessment the sensitivity of the CBA results to these parameters would be evaluated. We limit our discussion in this paper to vaccines that prevent infection, but it is important to note that efforts are also under way to develop vaccines that strengthen the immune system's response to established disease. Recent animal trials have generated hope for the prospects of this type of vaccine (Maurice, 2011).

examined the proposition that accerlated investment in AIDS vaccine development would have high benefit relative to cost – and hence justify diversion of resources from less productive development assistance investments.

The current and likely future sources of funding for vaccine development come from parts of the public sector that differ from those that fund AIDS control. Private sector product development funds likewise do not come at the cost of control money. Only in foundations is there likely to be genuine fungibility between product development resources and control sources. In this environment the CC12 role is perhaps not that of trading off vaccine development resources with resources for attractive control options. Rather a conclusion that the economic attractiveness of a continued vaccine development effort is high relative to other development assistance options would be *signaled* by perhaps modest allocation of control resources to vaccine development by the expert panel. That new products such as potential AIDS vaccines constitute international public goods – unlikely to be domestically financed by developing countries – is an additional factor. The RethinkHIV paper compared continued vaccine development efforts to a base scenario of discontinued funding and it also estimated what the benefits would be if additional funding were to reduce the time until a vaccine becomes available. The RethinkHIV panel placed accelerated vaccine development at the top of its list of priorities, and this CC12 challenge paper places it on the short list of 6 solutions, replacing expansion of combinations of existing means of prevention.

Hecht and Jamison (2011) assessed the consequences of scaling up funding to reduce the amount of time it takes to develop an AIDS vaccine. They assumed modest but real time savings from an additional $100 million dollar expenditure per year (over the approximately $900 million/year current rate of expenditure). The $100 million figure was based on interviews with

vaccine experts, who argued that the award of 5 to 10 packages of $10-20 million a year over a decade to carefully selected research consortia would substantially accelerate progress. They assumed that an 11% increase in vaccine R&D ($100 million more each year) would correspond to a shortened time to product launch of 0.4 to 1.0 years (with much uncertainty). Assuming first a 1.0-year gain, the time to vaccine approval would be 18 years as opposed to 19 years in the base scenario. This implies that an additional $100 million dollar expenditure per year would increase the total discounted funding requirement from $13.9 billion to $15.4 billion. However, shortening the time to approval would also decrease proportionally the number of years in which one would have to pay development costs. Because of this shortened period of expenditure, the (discounted) funding requirement would result in a net increase to $14.6 billion. The calculation of discounted R&D financing for accelerating vaccine development by 0.42 of a year follows the same steps as the ones outlined above.

What would be the benefits of such accelerated vaccine development? To calculate this, they used the estimated benefits from receiving the vaccine in 2030 (or in 2040, under alternative assumptions about product launch), then calculated the incremental benefit associated with accelerating the time to vaccine development by 1.0 or 0.4 years. They found that for a $5,000 VSLY and a 5% discount rate, the benefits of advancing the approval time by years is $73.5 billion (or $29.3 billion when the time gain is 0.4 years). From there, we estimate the benefit:cost ratio with sensitivity analyses around the VSLY and the discount rate. Even in the most conservative case of a $1,000 VSLY, a 3% discount rate, and a 0.4 year advance, the benefit:cost ratio exceeds 6:1. Table 6 displays the benefit:cost ratio of accelerating vaccine development under alternative assumptions. These findings make a strong case for increased funding to AIDS vaccine research and development, even though there is

great sensitivity in B:C to the underlying assumptions. For CC12 we assume a $1000 VSLY, a 5% discount rate, and an intermediate reduction in time to vaccine availability implying a B:C of 11:1.

Table 6: Hypothetical B:C Ratios from Advancing Time of Vaccine Availability

Value of statistical life year (VSLY)	Discount rate, per year	Years sooner that vaccine is available	
		1.0	0.4
$1,000	3%	26:1	6:1
$1,000	5%	18:1	4:1
$5,000	3%	106:1	22:1
$5,000	5%	71:1	16:1

Source: Hecht and Jamison (2011).
Note: Entries in the table are benefit:cost ratios.

5.3 Antiretroviral Treatment of AIDS

A primary focus on prevention strategies in the global response to HIV/AIDS reflects the fact that the future of the pandemic lies with those not yet infected. However, this cannot be taken as a reason to neglect the 33 million people currently living with the infection, two thirds of them in Africa. Prophylaxis or treatments for some of the opportunistic infections that contribute to HIV/AIDS mortality are cost-effective (most notably antibiotics effective against TB). Since 1996, highly active antiretroviral therapy has increased the life expectancy of people on treatment considerably. In developed countries, antiretroviral therapy has dramatically reduced but not eliminated AIDS mortality. Reduction in viral load slows or halts progression of AIDS and can return individuals from serious illness to reasonable health. Available drugs leave a residual population of HIV in the body, however, and this population grows if the drugs stop. At present the drugs must be taken for life. Widespread use of these drugs in high-income (and some middle-income) countries has transformed the life prospects of HIV-infected individuals and the RethinkHIV paper on treatment (Over and Garnett, 2011) found an attractive benefit to cost ratio for expanded treatment.

Early generation antiretroviral drugs suffered notable shortcomings: they were enormously costly; regimens for their use were complicated, making adherence difficult; their use generated unpleasant side effects; and rapid evolution of HIV led to resistant mutants that undermined the efficacy of therapy. In a remarkably short time scientific advances have substantially attenuated those problems, making feasible, at least in principle, antiretroviral therapy in low-income settings. WHO's "3 by 5" program had as its objective, for example, to reach 3 million people in low- and middle-income countries with antiretroviral therapy by 2005.

That goal was met (by 2007) and the global effort to make treatment widely available is well under way. An important contributor has been the Clinton Foundation's effort to negotiate reductions in the prices of first-line drugs and, more recently, second-line drugs.

Despite the indicated progress against the problems with antiretroviral drugs, challenges to their effective use in low-income environments remain formidable. The complexity of patient management is very real. Management requires high levels of human resources and other capacities in many of the countries where those capacities need to be most carefully rationed. Perhaps in consequence, achieving effective implementation has been difficult on even a limited scale. Bertozzi and Padian et al. (2006) review those problems and how they might be addressed.

Three points concerning widespread antiretroviral drug use are particularly noteworthy:

- Poor implementation (low adherence, development of resistance, interruptions in drug supplies) is likely to lead to very limited health gains, even for individuals on therapy. (This outcome is unlike that of a weak immunization program in which health gains still exist in the fraction of the population that is immunized.) Poorly implemented antiretroviral drug delivery programs could divert substantial resources from prevention or from other high-payoff activities in the health sector. Even worse, they could lead to a false sense of complacency in affected populations: evidence from some countries suggests that treatment availability has led to riskier sexual behavior and increased HIV transmission. The injunction to "do no harm" holds particular salience.
- Unless systematic efforts are made to acquire hard knowledge about which approaches work and which do not, the likelihood exists that unsuccessful implementation efforts will be continued without the appropriate reallocation of resources to successful

approaches. Learning what works will require major variations in approach and careful evaluation of effects. Failing to learn will lead to large numbers of needless deaths. Most efforts to scale up antiretroviral therapy unconscionably fail to commit the substantial resources required for evaluation of effects. Such evaluations are essential if ineffective programs are to be halted or effective ones are to receive more resources. While this point about learning from evaluation applies more generally, it is particularly salient for AIDS treatment.

- Many programs rely exclusively on the cheapest possible drugs, thereby risking problems with toxicity, adherence, and drug resistance. From the outset a broader range of drug regimens needs to be tested.

Use of ARVs is likely to have a B:C ratio greater than 1 in many circumstances. However if it competes with other highly attractive health investments in environments with limited human and financial resources, widespread adoption needs to be carefully sequenced.

6. Control of Tuberculosis

Tuberculosis is the leading cause of adult death from infectious disease after HIV/AIDS. Nearly 9 million new cases and perhaps 1.6 million deaths were caused by tuberculosis globally in 2003, with over 90% of these in low and middle income countries. Tuberculosis, like HIV/AIDS causes deaths in productive working age, and can thus be a trigger into household poverty. Only a small percentage of those infected with the tuberculosis bacillus go onto to active disease such as pulmonary tuberculosis. Key risk factors for active tuberculosis include poverty, household crowding, and smoking (Pai et al, 2006).

TB can be controlled by preventing infection, by stopping progression from infection to active disease, and by treating active disease. The principal intervention is the 'directly observed therapy, short-course' (DOTS) strategy and its variations, centered on the diagnosis and observed treatment of the most severe and most infectious (smear-positive) forms of TB but including treatment for smear-negative and extrapulmonary cases as well. Anti-TB drugs can also be used to treat latent infection and active TB in patients with HIV coinfection. The widely used BCG vaccine prevents severe forms of TB in childhood (Dye et al, 2006).

The cornerstone of TB control is the prompt treatment of active cases using first-line drugs, administered through the DOTS strategy which has five elements: (i) political commitment; (ii) diagnosis primarily by sputum-smear microscopy among patients attending health facilities; (iii) short course chemotherapy with 3-4 drugs including effective case management (including direct observation of treatment); (iv) a regular drug supply; and (v) systematic monitoring to evaluate the outcomes of every patient started on treatment.

The MDGs call for halting and beginning to reverse new cases of TB by 2015 and the Stop TB Partnership calls for halving prevalence and deaths by 2015 relative to 1990 rates. It has been estimated that these goals can be reached if 70% of new infectious (smear positive) cases worldwide are detected and 8% of those cases are treated successfully with the DOTS regime.

WHO and others have focused their operational efforts in high burden countries, and progress has been impressive. The case detection rates has increased from 11% globally in 1996 to 53 percent in 2004 and over 21 million TB patients were treated in DOTS programs in the decade since 1994. China and India have been noted as having particularly strong programs-although rigorous evaluation of the mortality impact of TB programs awaits. Key challenges remain the spread of HIV infection in parts of Africa and drug resistance, especially in Eastern

Europe. This suggests that DOTS alone might not be able to bring TB under control, especially in Africa and in the countries of the former Soviet Union.

The cost-effectiveness of tuberculosis control has been well established (summarized in Dye et al, 2006), but more recently Laxminarayan et al (2007) have calculated the cost-benefit of the WHO DOTS strategy at current levels relative to having no program in place. This finds that using statistical value of life of roughly 100 times per capita GDP, the net gain is about $1.7 trillion versus program costs of $18.3 billion in the 22 high burden countries. The ratio of marginal benefits of implementing a global plan for DOTS versus to their costs to be a factor over 15 in the 22 high burden countries, and a factor of 9 in the Africa region. These estimates are thus in the plausible range with the values shown below.

The minor for change of the CC12 recommendation on TB relative to CC08 lies in an explicit concern for dealing with multidrug resistant (MDR) TB as an integral part of an overall control strategy. This helps preserve available drugs for continued use and it provides (partial) insurance against a disastrous breakout of MDR TB. However, addressing resistance increases costs, despite the long term insurance value, and the short term benefits in averted deaths are limited. Although TB treatment remains on our solutions list it appears slightly less attractive than before for reason of cost.

7. OPPORTUNITIES FOR DISEASE CONTROL

The preceding three sections identified a range of attractive options for disease control based, for the most part, on the 315 interventions that DCP2 reviewed (Jamison, et. al. 2006). Laxminarayan, et al. (2006) summarized DCP2's main findings on cost-effectiveness which form the basis for the cost-benefit analyses reported here. One thing that is clear in the summarization of the cost-effectiveness information is that there is a broad range of reasonable estimates for most interventions. This is partly due to incomplete information and uncertainty. Even more importantly, it is also due to the responsiveness of the cost-effectiveness function to variations in prices, to the scale of application of the intervention (and of its substitutes and complements), and to the epidemiological environment.

Given these often broad ranges in CE ratios, and hence in cost-benefit ratios, it makes little sense to conclude with precise estimates of uncertainty or effect size. Rather we have identified 6 solutions for investment in interventions that address a large disease burden highly cost effectively even granted substantial uncertainty and variability in the underlying estimates. Even valuing DALYs at a conservative $1,000 and, again conservatively, reducing by 50% the DALY loss associated with an under-5 death (this affects the malaria and immunization numbers) the benefit to cost ratios associated with investing in these opportunities is enormously high. In Appendix A we provide a brief assessment of the sensitivity of our findings to key assumptions.

This concluding section provides three summarizing tables on our 6 solutions. Table 7 summarizes what the solutions consist of and the sources of our economic evaluations. Table 8

summarizes our results in a simple dashboard and Table 9 relates our conclusions to conclusions in related areas of CC08.

Table 7 presents our solutions. Three are interventions in the traditional sense (those dealing with TB, immunization and deworming). One is a pricing policy instrument (AMFm), one is a product development investment (HIV vaccines) and one is a platform carrying multiple, diverse interventions (essential surgery). All promise extraordinary benefit for cost. Two of the six solutions are preventive (the two dealing with vaccines) and the other four provide treatments.

Table 8 is presents a 'dashboard' rather than a league table to summarize our solutions. Every opportunity in the table has not only a very high estimated B:C but, also, addresses major disease burden. The interventions that would address the most DALYs are TB treatment (#1) and district hospital surgery (#5). Both would provide relatively a high degree of financial protection to populations.

Table 9 compares the results in Table 8 to those of CC08 and shows substantial carryover. The early success of the AMFm and increasing signs of promise in AIDS vaccine development led to their inclusion for CC12.

Table 7: Summary of Solutions

Solution	Economic evaluation
1. Tuberculosis treatment. This solution involves expansion of coverage of the WHO-recommended treatment algorithm DOTS (directly observed therapy, short course). Despite the label 'short course' treatment requires 6 months of observed drug use with concomitant expense, but DOTS has proved highly effective in practice in reducing mortality. For CC12 we include attention to dealing with multi-drug resistance TB (MDR-TB)	Cost-effectiveness numbers are drawn from *DCP2* (Jamison et al, 2006). The resulting cost per DALY is converted to a BCR by valuing a DALY at $1000 (or $5000). See also Laxminarayan et al (2007)
2. Malaria. Support for AMFm The two previous mainline antimalarial drugs, Chloroquine and SP, lost efficacy in much of the world in the 1990s because of resistance. Both drugs were highly efficacious and inexpensive, whereas artemisinin derivatives although effective are far more expensive. The Affordable Medicines Facility malaria, AMFm, operates from the Global Fund to provide manufacturers subsidies for artemesim in combination with another drug in order to provide access to the effective treatment while undercutting prices of monotherapies.	Cost-benefit analyses match total costs, including subsidies, against the DALY gains (drawing on *DCP2*) then convent to dollar benefits at $1000/DALY. See also Laxminarayan et al (2010).
3. Childhood immunization. This solution involves increased coverage of the six vaccines in the WHO-designated 'Expanded Programme on Immunization'	Cost-benefit analysis are based on *DCP2* cost-effectiveness analyses with DALYs valued at $1000
4. HIV: accelerated vaccine development. This solution involves increasing the rate of expenditure on HIV vaccine development from about $500 million per year to about $1 billion per year.	The cost-benefit analysis was undertaken for the CC RethinkHIV project using methods like those of CC12.

5. Essential surgery: This solution involves strengthening surgical capacity at the district hospital to better deal with trauma, obstructed labor.	Cost-benefit analyses are based on *DCP2* cost-effectiveness analyses with DALYs valued at $1000.
6. Deworming schoolchildren Over a billion individuals are infected by intestinal worms for which there is inexpensive, highly effective drug treatment. Child are the worst affected. Reinfection entails the need for continual deworming at a rate of once or twice a year. Great heterogeneity in intensity of infection implies similar heterogeneity in benefits which are here measured in increased quantity of schooling valued in terms of its impact on subsequent earnings.	Cost-benefit analyses for deworming are drawn but (subjectively) modified from those of CC08. The CC08 education paper (Orazem, Gewwe, and Patrinos, 2008) assessed deworming schoolchildren and the malnutrition paper (Horton, Alderman and Rivera, 2009) assessed both school-based and community-based (for younger children) deworming. Numbers here follow the nutrition paper more closely.

Table 8: DISEASE CONTROL: INVESTMENT SOLUTIONS

Solution	Indicative benefit-cost ratio	Level of capacity required	Financial Risk Protection Provided	Relevance for development assistance	Annual costs ($ billions)	Annual benefits
1. Tuberculosis: appropriate case finding and treatment, including dealing with MDR TB	15:1	M	H	M	1.5	1 million adult deaths averted or 30 million DALYs
2. Malaria: subsidy for appropriate treatment via AMFm	35:1	L	M	H	0.3	300,000 (mostly child) deaths averted or 10.5 million DALYs
3. Childhood diseases: expanded immunization coverage	20:1	L	L	L	1	1 million child deaths averted or 20 million DALYs
4. HIV: accelerated vaccine development	11:1	L	H	H	0.1	24% reduction in HIV incidence 15 years after introduction
5. Essential surgery: to address difficult childbirth, trauma and other	10:1	H	H	H	3	30 million DALYs
6. Deworming schoolchildren	10:1	L	L	L	0.3	About 300 million children dewormed

[a] This refers to level of capacity required for implementation in a developing country. While HIV vaccine development, for example, requires enormous scientific capacity, that capacity is functionary already where the development work would be undertaken.

Table 9: Infectious Disease, Injury and Reproductive Health: Solutions in CC08 and CC12

Solution in CC08	Expert Panel ranking in CC08 (out of 30)	Related solution in CC12, Infectious diseases, reproductive health and injury chapter
1. TB treatment	13	Very similar but with more explicit emphasis on the need to treat multi-drug resistant (MDR) TB as part of the treatment package
2. Malaria: package of treatment and preventative measures	12	CC12 provides a much more focused malaria recommendation: financial support for the Affordable Medicines Facility malaria (AMFm), which provides manufacturer level subsidies for antemisin combination therapies (ACTs). By reducing the price of a resistance-postponing combination therapy the AMFm makes effective treatment affordable and undercuts prices of resistance-inducing monotherapies.
3. Childhood immunization	14	No change between CC12 and CC08
4. HIV: combination prevention package	19	CC12 proposes the rate of expenditure on HIV vaccine development. This recommendation was ranked number 1 by the CC Rethink HIV Expert Panel.
5. Injury, difficult childbirth: Invest in surgical capacity at district hospital	21	No change between CC12 and CC08, except to be relabeled as 'essential surgery' to reflect current nomenclature.
6. Deworming children at schools[a]	6	Little changed between CC12 and CC08.

[a] For CC08 deworming was addressed in both the education and the nutrition challenge papers. The decision was made for CC12 to have deworming be addressed by this challenge paper.

With the exception of surgery in the district hospital, the opportunities identified don't explicitly address the strengthening of health system capacity. (Option 2, support for the AMFm, can in part be viewed as a substitute for strengthening capacity.) It will be important to ensure that implementation includes related investments in manpower and institutions, with 'related' broadly defined. (By using long-term average costs for the cost-effectiveness analysis, these issues were implicitly, although mechanically, dealt with.) One might consider there to be two broad approaches to strengthening health systems. One involves relatively non-specific investments in capacity and reforms of process. The second relies on learning by successfully doing and involves creating specific capacity to deliver priority services in volume and with high quality. In the second model, capacity strengthening spreads out from high-performing initial nodes. The approach that this paper implicitly advocates is very much in the spirit of the latter.

From national perspectives the interventions on TB, on essential surgery, and on immunization and on malaria treatment appear as very high priorities. Given that, for whatever reason, these interventions remain underfunded, there is a reasonable argument that development assistance funds should address these needs and to an important extent they do (through the very substantial resources of GAVI and the Global Fund Against AIDS, Tuberculosis and Malaria).

Most valuable interventions are familiar interventions with only modest international externalities. There is a reasonable argument that development assistance should finance international public goods such as R&D (eg AIDS vaccine development) and help reduce the risks of adopting new areas of public investment (eg essential surgery in many countries). Development of resistance to effective drugs in one country generates very substantial negative externalities affecting all others. AMFm, proposed by an IOM committee Kenneth Arrow, explicitly addresses these negative externalities through pricing mechanisms that work through

both the public and private sector. International support for TB control indirectly addressed these negative externalities by attempting to diffuse appropriate drug use protocol.

In CC08 TB treatment stood out as perhaps the most important investment on grounds of its high B:C, its high level of financial risk protection, its moderate systemic requirements and in the size of disease burden potentially averted. Because of the explicit recognition in CC12 of the costs of dealing with MDR TB we now list it overall on par with the other 5. Each of the other solutions have advantages and disadvantages relative to each other and different individuals might well order them differently. Our most general conclusion, however, is that even if all costs were increased by a factor of, say, 3 there is a substantial and very specific list of major and highly attractive investment opportunities for dealing with infectious disease, reproduction health and injury. Table 9 compares the solutions proposed for CC12 with those proposed for CC08.

Appendix A: Sensitivity Analysis

The analysis upon which we based the conclusions reported in Table 8 were undertaken under the following assumptions:

1. The discount rate is 3% per year and the version of the DALY that was used us based on this 3% and no age weighting. These are the assumptions used in the most recent presentation of methods, data sources and results on the global burden of disease (Lopez et al, 2006a, 2006b). Earlier tabulations of disease burden used age weighted DALYs which give broadly similar results except that somewhat more weight is given to conditions of middle age (TB, maternal deaths, trauma, psychiatric illness).

2. Chapter 6 (Jamison, et al, 2006) of Lopez et al (2006a) points to the mathematical impossibility of having the standard formulation of a DALY give a loss from a death at age 25 that that is more than 20% greater than the loss from a death at age 1 day. An alternative version of the DALY is proposed there [DALY (3,0, .54)] and used in this chapter. The effect is to reduce the DALY loss of a death under age 5 by about 50% without changing the DALY loss from deaths at older ages.

3. In an attempt to include relevant health systems costs and to take a long-run view, cost estimates in this chapter as based on long-run average costs (at least in principle as there is some variation in actual costing methods).

4. Cost analyses in this chapter assumes zero deadweight losses from taxation, but the analyses in this Appendix explore sensitivity to their valuation

5. The chapter assumes the value of a DALY or of a VSLY to be $1000.

Appendix Table A1 reports assessments of the robustness of our conclusions with respect to changes in these assumptions. On the most optimistic alternative assumption of Appendix Table A1 the B:C for immunization and for malaria would increase by a factor of 10; for the other interventions the factor is 5. Taking the least optimistic assumptions the B:C of all interventions would decline by a factor of 10.

If the B:C is being used by a government to decide whether to fund the relevant health programme compared with other programmes or saving the money, it should adjust the value of a DALY in line with its GNI per capita. To do so, it should multiply it by its GNI per capita and divide by 500. The B:C will move by the same factor.

If the B:C is being used to compare the interventions in this chapter with interventions that affect people in richer countries, it needs to be significantly increased to avoid discounting the value of the health effects just because they accrue to the world's poorest people. To do so, multiply the B:C by the GNI per capita of the country for whose citizens the willingness to pay of the other interventions was estimated and then divide by 500. This could increase these ratios by as much as a factor of 100. Note that the '500' in each of these is because that is the current implicit estimate of the country's GNI per capita, so if you change the $1000 per DALY figure,

you would want to adjust these proportionally. e.g. if you use $1500 per DALY, then make these 750.

Appendix Table A1: Sensitivity Analysis

Change in assumption	Consequence
1. Change the discount rate from 3% to 6% per year, i.e. change to DALYs (6, 0, 0.54)	The number of DALYs gained from each of the interventions and hence B:C will decline by about 50%.
2. Change from DALYs (3, 0, 0.54) to DALYs (3,0)	The number of DALYs gained from immunization and from malaria control will approximately double, as will the B:C for the related interventions.
3. Since *ex ante* costs are typically underestimated, often substantially, multiply all costs by 3.	B;C will decline to 1/3 of its otherwise estimated value for all interventions.
4. The deadweight loss from taxation is increased from 0 to 50% of the revenue raised (Ballard, Shoven and Whalley, 1985, provide estimates in this range.)	B:C value declines by 1/3.
5. The value of a DALY is $5000 rather than $1000.	B:C values go up by a factor of 5.

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