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A Framework for Developing a Research Agenda for Diseases Disproportionately Affecting the Poor:

The Cases of Malaria, Diabetes and Rotavirus

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EXECUTIVE SUMMARY

Introduction

In this paper, we consider three diseases -- malaria, diabetes, and rotavirus -- selected because of their contrasts. Parasitic, viral and noncommunicable diseases all have a major impact on health in developing countries, though the nature of the challenge they present, and consequently of the tools needed to address them, vary considerably. These contrasts can illuminate key issues that should be considered in making proposals that are meaningful across a range of conditions, which potentially fall under the umbrella of diseases relevant to the Commission.

Malaria, diabetes and rotavirus have, it can be argued, more contrasts than comparisons. They represent a small sample of diseases with a considerable burden in developing countries, and suggest the very different nature of the problems -- and viable solutions -- at issue with regard to their management and control.

Disease Case Studies

Malaria is caused by *Plasmodium* parasite, a multi-cellular organism with a complex life cycle against which several weapons currently exist, but which is still a major scourge of the poor. This is, in fact, one of the notable features of malaria: that its prevalence is strongly focused on the poorest countries, and within these countries, on the poorest segments of society. The correlation between the likelihood of getting the disease and poverty means that there are important challenges in terms of reaching the affected communities, both with interventions and with the informational and human resources that could protect them. Nevertheless, malaria has become a high profile disease: the meeting in Abuja of African leaders 1996, followed by the establishment of the Roll Back Malaria Partnership in 1998, the Millennium Development Goals in 2000, and the Global Fund for AIDS, Tuberculosis and Malaria in 2002 have created a momentum, and put malaria back in the spotlight. Most important, this impetus has led to increased political and financial support for coordinating malaria's treatment and control in those countries left out of the early eradication campaigns. While there is considerable progress, important barriers remain. For instance, the use of bed nets remains below desirable levels, and as a result the most at-risk groups -- namely women and young children -- are still very exposed. The reason seems to be a failure to make the use of bednets an accepted and acceptable norm in communities. There are also technical and political challenges, for example those relating to the use of insecticides, such as DDT, and the cost barrier to accessing the most effective antimalarial drug (ACT). The good news, however, is that a range of products does exist which have been specifically developed for use in low-resource settings; many of the challenges are with regard to health systems and the scaling-up of control programmes, though there remain important technical obstacles such as creating a synthetic version of artemisinin, and the development of an effective vaccine.

Diabetes is an obvious contrast in nearly every respect -- first, because it is a disease that affects the rich as well as the poor, and second because, while there do exist a number of

interventions, from chemoprophylaxis to surgical intervention for its treatment, none of these has been created for use in poorer markets. The environmental and genetic factors that contribute to the disease are complex, and correlate strongly to lifestyle, including as diet and physical activity. An important difficulty is getting the message across that it is a disease that affects a growing number of people in developing countries. One of the critical issues relates to low-income countries' ability to address the so-called double burden of disease -- that is, the reality of a high burden of infectious disease alongside a considerable burden of noncommunicable conditions, of which diabetes is an important example. Researchers in both the public and private sectors around the world devote considerable energy to the creation of new products to treat or prevent diabetes, as well as towards science that improves our understanding of its cause. But almost no work is systematically devoted to creating new tools, or modifying existing tools, for use in resource-poor settings, the consequence being that their benefit is hardly felt.

Rotavirus infection is one of many causes of severe diarrhoea is young children. Unlike malaria, it is ubiquitous, affecting nearly all children in every part of the world by their third birthday. But poor children, because they are malnourished and may be co-infected with other diseases, experience a disproportionate degree of morbidity and mortality. ORT, described by researchers in the 1960s, was a critical achievement for the control of diarrhoeal diseases, generally. Moreover, probiotics have been suggested as low-cost ways of decreasing the severity of diarrhoeal episodes, including those caused by infection with rotavirus. Alongside these approaches, the major research agenda has clearly targeted a single goal for decades: the quest for an effective childhood vaccine. Because rotavirus infects children everywhere, it is not thought that sanitation and environmental factors, such as clean water, play the large role they were once believed to, and drugs have had very limited success. A preventive vaccine therefore has been the holy grail for rotavirus control. But a vaccine presents its own important challenges. For instance, there is a practical obstacle, namely that the efficacy of the most promising vaccines, for instance Rotarix, declines along with socioeconomic status of the country in question: from 99% in the United States, to 97% in Latin America, 70% in Asia and 50% in Africa. More generally, there is the difficulty of integrating a rotavirus vaccine into the existing vaccine schedule. There are particular challenges to making a vaccine for children in these markets, including their poor nutritional status, exposure and possible co-infection with other diseases, and exposure to other treatments. Even in the event that a highly effective vaccine with wide-scale coverage is created, rotavirus is one of several causes of diarrhea; children protected by the vaccine will be spared one or two severe rotavirus-induced bouts of diarrhea, but will still be susceptible to infection by shigella, cholera, typhoid or any other diarrhoeal agent prevalent in their area. While this still represents important protection, parents may not see or understand the full weight of its benefit, in view of the remaining diarrhea burden, and consequently be turned off vaccines because of perceived ineffectiveness. This could have an impact on their views of vaccines more generally.

Discussion

Malaria, diabetes and rotavirus have a significant impact on the poor for diverse reasons that relate to the very different causes, manifestations, impact and available treatment options for

each condition. Here, a framework is proposed to examine the features of key interventions for each of these conditions within a framework. It borrows from a human rights approach, and focuses in on four dimensions of the issue: availability, accessibility, acceptability, and quality. 'Availability' requires that health products and services be on hand in *sufficient quantities* within a country, including the question of whether the needed intervention exists in the first place. 'Accessibility' requires that all sections of the population, without discrimination, be within physical reach and able to afford them. For simplicity, we focus here on the affordability component of this dimension. 'Acceptability' relates to the degree to which interventions are ethically and culturally appropriate, and 'quality' refers to their scientific and medical appropriateness. Such a framework can be useful for analysis by helping to differentiate in a systematic way the various reasons an intervention may fail to adequately benefit the poor. It can also help in identifying and categorizing potential solutions appropriate for the problems that predominate for a given intervention. Finally, the schema suggests how to frame problems and to identify appropriate solutions *given existing social and economic inequalities*. The inequalities themselves remain outside of the schema and outside of the scope of what this Commission can address, but through such a framework they nevertheless inform proposals that take sufficient account of these realities to be meaningful and even practical.

Conclusions

- ***Most diseases*** **disproportionately affect developing countries.** There are several reasons for accepting an expansive view of the diseases that fall under the remit of the Commission. First, the Commission does not give up anything if it accepts an expanded view; it is still addressing neglected (and very neglected) diseases if it addresses the much larger set of conditions that contribute to mortality and morbidity among the poor. Moreover, a broader understanding of what is captured by "disproportionate" takes a more forwarding-looking view, and acknowledges the social, economic and demographic trends that are profoundly affecting the disease burden in developing countries. Finally, a human rights and equity (as well as standard public health) arguments insist on giving consideration to the underlying determinants of health in the allocation of scarce resources -- including resources for health-related research -- and thus considering the inter-related factors, both social and scientific, that contribute to unequal health.

- **Improving "access" is not enough.** "Access" alone is an inadequate determiner of the extent to which interventions reach the desired groups. Very often, the term "access" is employed in a manner that can easily confound problems that are of fundamentally different kinds, and impede the application of appropriate remedies. A model which considers the four dimensions of *accessibility, availability, acceptability* and *quality* provides a useful framework for systematically analyzing the nature of the challenges that exist, as well as their possible solutions. This schema, which is commonly used within human rights analysis to assess the extent to which governments are fulfilling their obligations, frames the problem in a way that could point the Commission to the particular gaps and challenges that exist for different conditions, and to appropriate remedies. In addition, it emphasizes the degree to which vulnerable or poorer groups

benefit from interventions. It is therefore one that links products with key features of poverty, and puts the lens on groups of principal interest to the Commission.

- **Research is a critical part of nearly every phase of the 'discovery to delivery' chain.** Diseases can have a disproportionate impact on developing countries because no effective treatment exists, or because effective treatment exists but is clinically sub-optimal; inadequate supply to implement on a large-scale; too costly to be afforded by low-income groups; less effective, ineffective or of unknown effectiveness in vulnerable groups; inadequate on its own; or impractical for use in low-income settings.[1] Research of various kinds is therefore essential to addressing the impact of these diseases, including to understand better the basic etiology of the disease, to identify possible targets for improved diagnosis / treatment, to create all-new interventions, and to modify existing treatments so that they are effective in sub-optimal settings.

  'Delivery' concerns should be part of decision-making early in the R&D process. Malaria, diabetes and rotavirus provide good examples of the role of research across the 'discovery to delivery' chain. Thinking about the challenges of distribution and delivery needs to start as early in the research chain as possible. It cannot be taken for granted that, once created, a product that shows efficacy under trial conditions will prove effective in the more rugged conditions that characterize many developing countries. Effectiveness is a more relevant measure, and takes into account both intervention's efficacy and its acceptance to those for whom it is intended, under routine conditions.

I. INTRODUCTION

This paper has been prepared as a background for the Commission on Intellectual Property Rights, Innovation and Public health, which has been asked by WHO's Member States to "...produce an analysis of intellectual property rights, innovation and public, including the question of appropriate funding and incentive mechanisms *for the creation of new medicines and other products against diseases that disproportionately affect developing countries*".[2,3] The value of new drugs or vaccines or other interventions depends on a great number of factors, including the particular features of the disease in question as well as the effectiveness of existing interventions, given biological and social realities.[4]

In this paper, we consider three diseases -- malaria, diabetes, and rotavirus -- selected because of their contrasts. Parasitic, viral and noncommunicable diseases all have a major impact on health in developing countries, though the nature of the challenge they present, and consequently of the tools needed to address them, vary considerably. These contrasts can illuminate key issues that should be considered in making proposals that are meaningful across a range of conditions, which potentially fall under the umbrella of diseases relevant to the Commission.

Ultimately, these diseases serve as case studies for considering the particular issues confronting the Commission in its analysis relating to products relevant to "diseases disproportionately affecting developing countries". Given the remit of the Commission, this paper is explicitly concerned with the status of existing interventions as well as research strategies *from the perspective of developing countries*. Each case study consists of a review of existing interventions, their effectiveness and coverage by highlighting significant achievements and challenges; a review of the current status of the global research agenda to generate new products, including a discussion of major actors; a short discussion of existing mechanisms for the procurement of interventions, which addresses an additional dimension of the "access" question; and finally, a conclusion pointing to trends, making tentative proposals, and suggesting a useful model for analysis. More particularly, the final chapter of the paper considers what issues can be drawn from the three case studies, in terms of clarifying how to characterize "diseases that disproportionately affect developing countries" in a way that can meaningfully inform research and innovation strategies.

Malaria, diabetes and rotavirus: Diseases that disproportionately affect the poor?

The Millennium Development Goals, adopted by 189 heads of state in 2000, represent a historic commitment among nations to "a global partnership to reduce poverty, improve health, and promote peace, human rights, gender equality, and environmental sustainability".[5] Three of eight the goals, eight of the 16 targets and 18 of the 48 indicators relate directly to health.

Goal 6 is to combat HIV/AIDS, malaria and other diseases. In 1998 the international community, galvanized by the initiative of African leaders, was reawakened to the malaria tragedy that continued to affect parts of the world left out of the early eradication campaigns. In 1998, the Roll Back Malaria Partnership was established with the stated aim of halving the burden of by 2005, and African heads of state came together again in 2000 and committed themselves to a set specific targets for their countries.[6] One year later, the Global Fund to Fight HIV/AIDS, Tuberculosis and Malaria was created to "finance a dramatic turnaround in the fight against" these diseases and to "support aggressive interventions against all three".[7] These high-level commitments and new schemes have had an important impact in increasing global consciousness of a disease that continues to claim an estimated 1 to 2 million lives and to account for 300 to 500 million episodes of illness annually.[8]

Under Goal 4, the Millennium Development Goals include a target to reduce the mortality rate for children under five years by two thirds by 2015 compared to 1990. In 2002, the UN Special Session on Children produced "A World Fit for Children", pledging to reduce by one half the number of deaths due to diarrhoea among children under five years by 2010 compared to 2000, and at the World Summit for Children in 1990, over 150 countries undertook to attain 80% oral rehydration therapy (ORT) coverage by 1995 with a view to achieving a reduction of 50% in mortality attributable to diarrhoea by 2000.[9] Of all diarrhoeal diseases, rotavirus is the commonest among children, and though it is ubiquitous across the globe, it is particularly deadly for children living in poorer regions where more than 1000 die each day. In recognition of this, WHO's former Programme for Control of Diarrhoeal Diseases (WHO/CDD) in 1979 listed for the first time the prevention of rotavirus disease as one of its goals. Six years later, the United States Institute of Medicine (IOM) wrote that rotavirus vaccine development was a high priority for developing countries, and in 1996, rotavirus was listed as a "best buy" for developing countries in a major report.[10] Over the past decades, the disease has evolved, developing growing resistance to previously key drugs, and early gains have been eroded. But the emergence of public-private ventures and a promising pipeline of products for the prevention and treatment of malaria have renewed optimism that important progress can be achieved.

For its part, diabetes is projected to become one of the world's main disablers and killers within the next 25 years. An estimated 30 million people worldwide had diabetes in 1985, and within one decade the number swelled to 135 million.[11] According to the latest WHO estimates from 2000, there are 171 million people with diabetes worldwide, and prevalence is projected to climb to 366 million by 2025. Much of this increase will occur in developing countries. While there has been no global initiative for diabetes on the scale of the Millennium Development Goals or similar declaration by heads of states, diabetes associations and regional organizations in five regions (Eastern Mediterranean and Middle East, Europe, North America, as well as South and Central America and the Western Pacific) have signed declarations on diabetes in acknowledgment of the magnitude of the problem, spelling out strategic actions. These declarations are designed to implement national diabetes programmes, to improve the quality of diabetes care, to promote research and to raise public awareness about diabetes. At the global level, the International Diabetes Federation is collaborating with WHO to embark on a major course of action to raise awareness about

diabetes and its complication among the public, health professionals and decision makers, with major emphasis on prevention in low income countries.

From the above it is clear that these three diseases are widely viewed as important threats to health globally for people living in developing countries. In the remaining sections of this paper, we will consider where we are, in terms of interventions that exist today for their treatment and control; where we are going, in terms of the direction of global research; and how we might do a better of job of matching the two, in view of the specific needs of the poor.

II. TAKING A CLOSER LOOK AT DISEASES THAT DISPROPORTIONATELY AFFECT DEVELOPING COUNTRIES: THE CASES OF MALARIA, DIABETES AND ROTAVIRUS

1. MALARIA

Malaria is caused by a single-celled parasite of the genus *Plasmodium* that is spread to humans by a single vector: the anopheline mosquito. Four different species cause the disease: *plasmodium falciparum*, *plasmodium vivax*, *plasmodium malariae* and *plasmodium ovale*. *P. falciparum* is the major cause of death and disability, particularly in Africa and as such is now the target of most research. *P. vivax* is less fatal, but also debilitating and has an estimated burden of 70-80 million cases per year, 80-90% of which occurs in the Middle-East, Asia and Western Pacific, with the rest in Central and South America.[12] In addition to its direct role in causing morbidity and mortality, malaria is also believed to contribute to the effect of common conditions, like measles, respiratory infections, diarrhoeal disease and malnutrition.[13]

Until the end of the Second World War, malaria was endemic in many parts of the world, including Southern Europe, with regular outbreaks as far north as Scandinavia. Today, malaria is concentrated in tropical and subtropical zones, with 110 million Africans living in areas at risk for epidemics of malaria. The actual number of cases today is difficult to measure. Though almost all countries attempt to track malaria cases, the complexity of the disease makes it extremely difficult to disaggregate the data. Best estimates are that about 1.1 million deaths were attributable to malaria in 2000, with approximately the same number in 2001. 970, 000 of these were in Africa, and between 60 and 80% were among children under five years old. Published figures are, however, only rough estimates because of the difficulty in obtaining accurate data due to the enormity of the disease and the weakness of health information systems, among other factors.[14] The WHO Commission on Macroeconomics and health estimated that up to US$2 billion is needed each year to achieve the Roll Back Malaria partnership's goals of halving the burden of malaria by 2010.[15]

Eradication Campaigns

The Global Eradication Campaign, which took place between 1955 and 1964, succeeded in restricting malaria distribution by eradicating it from North America and Europe. During the Vietnam War in the 1960s, the United States (US) Government poured an unprecedented amount of funding into malaria research, when it became evident that American troops risked infection with malaria. For nearly fifty years, chloroquine (CQ) was used to successfully manage infection in most parts of the world as it was readily available and inexpensive. By 1966, campaigns using DDT spraying, elimination of mosquito breeding sites, and mass treatment had freed more than 500 million people from the threat of disease.[16] Following on from the success of the eradication campaign in the US and Europe, the World Health Organization (WHO) submitted an ambitious proposal for the eradication of malaria worldwide at the World Health Assembly in 1955. Eradication efforts began and focused on

house spraying with residual insecticides, antimalarial drug treatment and surveillance. Successes included eradication in nations with temperate climates and seasonal malaria transmission. Malaria was eradicated from the Soviet Union, southern Europe, the United States, all but one of Caribbean Islands, and Taiwan Province of China. Spread of the disease was also suppressed in several subtropical and tropical regions of southern Africa, Latin America, parts of Asia, and the Middle East. Tropical Africa was excluded from eradication campaign, because of the perceived intractability of the disease and concerns of sustainability; along with New Guinea, they are the only regions where malaria burden persists today.[17,18]

BOX 1. Basic Package of Interventions

- Long-lasting insecticidal nets free to high-risk population groups and replacing them after four years of use
- Introduce ACTs in all areas of significant p. falciparum transmission, rapid diagnostic tests where malaria is less intense and fevers are from causes other than malaria
- Provide sp-based intermittent preventive treatment to all pregnant women where malaria transmission is stable
- Ensure availability of adequate supplies of specific therapies and general clinical support to treat cases of severe complicated malaria
- Improve epidemic prevention and response capabilities, including enhanced surveillance systems and application of indoor residual spraying where malaria transmission is unstable
- Support particular elements of the health infrastructure that are critical for the efficient implementation of scaled-up antimalarial efforts (including transportation and lab equipment)
- Train community health workers and existing health facility staff in prevention measures, new treatment protocols, and diagnostics
- Produce and distribute community-directed strategic communications that reinforce knowledge of malaria prevention, early recognition of symptoms, and the need to seek treatment promptly
- Reduce critical gaps in human resources, including health professionals, epidemiologists, entomologists, and workers in other relevant technical fields

Mills, Shillcutt (2004)

Some say the biggest obstacle to combating malaria in Sub-Saharan Africa was the widespread distribution of *Anopholes gambiae,* a long lived and aggressive malaria-carrying mosquito. To illustrate, the entomological infection rate (EIR), which measures the frequency with which a human is bitten by an infectious mosquito, rarely exceeds five per year in Asia or South America; by contrast, EIRs of over 1000 have been recorded in several parts of sub-Saharan Africa[19]. Another determining factor was that the malaria parasite began to develop resistance against the existing front-line therapy chloroquine (CQ), and the mosquito's development of resistance to available insecticides, severely compromising the their efficacy.[20] CQ resistance started in Asia in the 1960s and 1970s, with the evolution of mutant parasite strains, and found its way to Africa in the 1980s. The growing failure of CQ and other low-cost drugs like sulfadoxine-pyrimethamine (SP) resulted in an increase in malaria-related deaths, after a period of declining mortality post-

Intervention	Annualized per capita cost	Total annualized cost (millions)
Insecticide-treated nets	8.12 per child	496
Intermittent preventive treatment	2.02 per pregnancy	10
Changing to ACT	0.83 per malaria case	140
Scaling up ACT	5.66 per malaria case	177
Total		**824**

Table 1. Estimated cost of basic package of interventions.

World War II. DDT, which was instrumental in the success of early eradication campaigns, was discredited because of concern about ecological damage and possible harm to human health, because it persists in the environment long after initial application.[21]

Recent experiences from around the world, including Brazil, Cambodia, Eritrea, South Africa and Vietnam, show that with the effective deployment of medication and prevention methods, malaria can be controlled.[22] In Eritrea control efforts by the Ministry of Health have demonstrated reductions in malaria mortality and morbidity for five successive years. The 60% decline in overall mortality from malaria was the result of a combination of approaches including free distribution of treated mosquito nets for all vulnerable populations with a special focus on under fives and pregnant women, indoor spraying and environmental management, and prompt and proper treatment of severe malaria[23]. Examples of the successful scale-up of malaria control can be found in Ethiopia, Madagascar, Viet Nam, South Africa and Tanzania -- all of whom employed an integrated package of effective malaria control interventions tailored to local context, along with effective programmes for monitoring and evaluation. These successes show the feasibility of effective control[24], but represent local achievements rather than large-scale progress.

WHO commissioned a study evaluating the global cost of malaria, in support of the Millennium Project Working Group on Malaria, which estimated costs for an accelerated global scale-up of a "basic package" (Fig. 2.) of standard antimalarial interventions to meet the Abuja targets by 2015 at US$ 31.86 billion, or about US$ 3 billion per year. The authors of the study point out that their data sources, which for malaria were very limited, have severe shortcomings. The figure of US$ 3 billion per year does not include estimates for the amount required to scale-up *production* of artemisinin. As we saw, according to the Institute of Medicine, this would mean an additional US$ 300-500 million per year for an undetermined period (IOM).

Social and Economic Dimensions of the Disease

There is a strong social and economic dimension to the malaria disease burden. *At present, 58% of malaria cases occur in the poorest 20% of world's population, a greater proportion than any other disease of major public health importance in developing countries.* Among the poor, the hardest hit are by far young children and pregnant women.

The direct and indirect costs of malaria are high. Poor families spend up to 25% of their annual income on prevention and treatment, without counting the more hidden costs of lost income and lost productivity due to sickness or even death. The effect of the economic burden of malaria is far reaching, holding back economic and social development. Indeed, it accounts for a reduction of 1.3% in the annual growth rate of malaria endemic countries, and that this represents a loss of nearly $100billion of GDP over 35 years[25]. Malaria also has an untold effect on children, who may experience long-term harm due to the illness. For instance, there is growing recognition of the "growth and development" burden of malaria, though is still a relative lack of understanding of its underlying cause.[26]

Major Achievements & Challenges in Malaria Treatment and Control

Diagnosis

In Africa, 70-90% of febrile events in children are treated at home without any medical diagnosis.[27] This means that children are often repeatedly exposed to potentially toxic drugs, with unclear long-term effects on their growth and development. Diagnosis is available, but requires microscopic analysis by trained technicians, good equipment and reagents. Because this is expensive and time-consuming, diagnosis is typically based on signs and symptoms, like chills, fever, diarrhoea, body aches -- which mimic many other common diseases. The result is 60% over-treatment and increased costs, in addition to potential health hazards due to excessive drug exposure and development of resistance.[28] Recently, a rapid and easy-to-use diagnostic test based on the plasmodium antigen detection on disposable dipstick has been introduced. But while it is sensitive, there is still limited information about its effectiveness.

Treatment

Traditionally, malaria has not attracted significant investment by private sector companies because even modestly priced drugs are unaffordable for lower-income countries. A comprehensive engagement in any area of modern drug discovery and development requires a huge investment of manpower and resources that needs to be matched by an adequate return. For diseases such as malaria, this return is not usually possible, though recent experience with Artemisinin-based drugs has shown that private sector investment can be successfully fostered. Nonetheless, most antimalarials developed in the past 50 years are the product of publicly funded R&D.

Because the drug R&D process needs more than just funds, but also considerable coordination and management coupled with specific areas of specific scientific and technical expertise, a crucial need has been identified for public-private sector partnerships to address the problem.[29] The creation of the United Nations Development Programme/World Bank/World Health Organization/Special Programme for Research and Training in Tropical Diseases (TDR) in 1975 facilitated the establishment of a partnership approach to drug discovery and development between public sector organizations and companies for those diseases lacking strong market incentives.[30]

BOX 2. "Wish List"

MMV has defined a target product profile: the ideal antimalarial drug should demonstrate efficacy against drug resistant strains, cure within three days, low propensity to generate rapid resistance, safe in small children, safe in pregnancy, appropriate formulations and packaging, and low cost. Such a "wish list" approach was employed by researchers who recently created a synthetic molecule to work the same way as artemisinin, but less expensive and easier to mass produce. Their work, supported by MMV and WHO, generated a product that has been successfully treated in animals, and appears to be more effective and longer-lasting than existing artemisinin-based treatments. The first human trials started in 2004 (IOM, 2004).

In the world of antimalarial drug research and development, there are three principal players: the Medicines for Malaria Venture (MMV), the UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR), and the Walter Reed Army Institute of Research (WRAIR) in the United States. MMV and WRAIR have set

targets of one new antimalarial every 5 years. MMV, TDR and WRAIR's combined annual funding needs today total US$60 million, a figure that will rise as more drugs enter clinical trials.[31]

In contrast to a few years ago when resistance was rising and few drugs were in the pipeline, the situation today has improved, with several new combinations and all-new classes of drugs under development. Thanks largely to the prominent work of public-private partnerships and companies like Novartis, as well as an injection of capital from the Gates Foundation, over the last ten years there has been a resurgence of activity and interest in the area of malaria drug and vaccine development. Moreover, the publication of the completed genome sequences for humans, the work of MMV, as well of the *P. falciparum* and *anopheles gambiae* have renewed optimism in new drugs and vaccines being developed.

In particular, with the emergence of drug resistance, new hope was found in artemisinin and its derivatives, compounds derived from the ancient Chinese herbal remedy *qinghaosu*, which comes from Artemisia annua, the sweet wormwood known to the traditional Chinese medicines used to treat fever for nearly 2000 years. In 1970, Chinese scientists isolated the active component, artemisinin, and developed it for the treatment of malaria. On the Thai-Burmese border, field studies using **artemisinin-based combination therapies (ACT)** were first undertaken in 1991 replacing mefloquine with mefloquibe-artesunate as first line treatment for symptomatic malaria substantially reduced the incidence of local infection[32]. But although it is less than US $2 per course, artemisinin is still ten times more expensive than CQ and unaffordable in the quantities needed to address the volume of 300 to 500 courses per year.[33] This cost owes largely to the fact that (despite recent progress) a synthetic version of artemisinin is not yet commercially available. In the meantime, the artemisinin herb must be grown and harvested, and the active ingredients isolated, prepared and packaged: a lengthy and costly process.

BOX 3. ARVs as Antimalarials

A study published in the *Journal of Infectious Diseases* in December 2004 shows evidence that protease inhibitors (6 commonly used ARVs) used to treat HIV-1 infection are also effective for treating and preventing malaria, by inhibiting the growth of the parasite. This work could improve knowledge of how to treat patients co-infected with HIV/AIDS and malaria with protease inhibitors, and could also lead to new type of malaria drug targeting the parasite in a novel way. The mode of action of the drug is still unknown, but the authors hypothesize that it involves the interruption of the parasite's digestion hemoglobin. This means that programmes like WHO's "3 by 5" could benefit patients at risk of parasitic infection. Studies on the role of ARVs as antimalarial drugs are still in their early stages, and being tested in vitro (Baragona, 2004).

There is broad consensus that the way to ensure artemisinin sustained effectiveness against malaria is to use it in combination with other drugs. These cocktails are called artemisinin-based combination therapies (ACT). The concept of combination therapy is based on the synergistic or additive potential of two or more drugs, which improves therapeutic efficacy and delays the development of resistance to the individual components of the combination. Artemisinin also has a short elimination half-life, so that therapeutic effects can be prolonged if it is partnered with another drug that has a longer blood half-life, such as lumefantrine.

Today, because of resistance, artemisinins are the only first-line antimalarials that can be used on a widespread basis, and work effectively against all CQ-resistant parasites. Consequently, in countries with proven resistance to currently used antimalarials, ACTs are recommended. The government of Zambia became one of the first countries in Africa to adopt ACTs in all formal health facilities. As a result about 75% will have access to the treatment.[34] In some countries, amodiaquine and SP are still useful and effective, but resistance is building. A critical research problem is that many of the studies on resistance have been carried out on children under five years, and some question whether these results can be generalized to adults, who experience the highest morbidity and mortality in in areas with stable malaria transmission. To-date Coartem (artemether-mumefantrine) is the only registered ACT. Since malaria is particularly severe in children, MMV has a project to develop a pediatric formulation of Coartem for infants and young children who are unable to take tablets.[35] Another artemisinin-based antimalarial drug, Artekin (dihydroartisinin-piperaquine), under development by international partners, has shown great potential. If managed well, ACTs could remain first-line antimalarials for many decades, but they will eventually lose their effectiveness. In the meantime, cheaper, more effective drugs could replace or combine with artemisinins at the front line.

The rapid increase in demand for ACTs in 2004 and the fact that it takes six to eight months for the plant from which artemisinin is extracted to grow, have contributed t o higher prices and temporary supply shortages. This may have been compounded by some farmers' withholding supplies from the market in a bid to drive up prices. Stabilizing prices at a lower level and production volumes at higher levels requires the recruitment of new producers. The continued overall lack of global demand, due to high cost, has resulted in slow production and impeded economies of scale as well as improved production methods. Wholesalers claim that with the assurance of a large market, prices could fall to US$0.50-1.0 within two years, though even this remains 5-10 times higher than the price of CQ in Africa (IOM, 2004). A real price breakthrough is unlikely until a fully synthetic drug becomes available; one is currently under development by MMV, and is predicted to be available in 5-6 years (IOM, 2004). In the meantime, switching to less expensive alternatives, like SP-CQ combinations, is not feasible because countries generally find it difficult to modify treatment policies proactively, and each change in treatment policy incurs costs. Immediate replacements for CQ and SP are amodiaquine and fixed dose combination of chlorproguanil and dapsone (Lapdap), but these already suffer from parasite-resistance in some countries, and safety has not been fully established. SP, the only antimalarial recommended for pregnant women, suffers from widespread resistance.[36] A major downside of ACT, too, is its unknown safety in pregnant women and women of child bearing potential -- populations at greatest risk of infection. Testing safety in the first trimester of pregnancy is a very difficult ethical and regulatory issue, as is testing safety in children and infants.

Encouraging results have been generated using antimalarial chemo-prophylaxis, including **intermittent preventive treatment (IPT)**, during pregnancy. IPT involves treating expectant mothers with antimalarials during their regular prenatal clinic visits, without first determining if they are infected, and has resulted in a clinically significant reduction of the levels of parasite in the blood. Results of two IPT studies in Tanzania showed a reduction in

the risk of malaria infection and a significant increase in healthy babies born to first-time mothers. At least two-thirds of pregnant women in 15 of 17 African countries attend antenatal clinics at least twice during their pregnancy, which provides an opportunity to deliver the IPT drug package.[37] By late 2004, an IPT policy had been adopted in 21 countries. In five of these, that policy is being implemented throughout the country or progress towards that goal is on track.[38] In Malawi where malaria is the leading cause of sickness and death, IPT was shown to reduce placental parasites by 33%, resulting in a reduction in the incidence of low birth weight decreased by 50%.[39,40] In Liberia, the overall incidence of malaria was also brought under control with the help of IPT in conjunction with indoor residual spraying, treated bednets and the improvement of diagnosis facilities within the refugee camps.[41] In an exciting but still insufficiently researched area, the use of **intermittent preventive treatment in infants (IPTi)** is being explored. Under this approach, children receive antimalarials three times during their first year of life, coinciding with obtaining their routine immunizations. In Tanzania, an IPTi study showed that clinical malaria was reduced by 60% and severe anaemia by 50% in children who received two treatments of SP during their first year of life.[42]

Large-scale programmes to deliver IPTs to pregnant women are only now being developed, and data on best practices and good logistics strategies to increase coverage in a sustainable manner are very limited. Surveys conducted on a national scale indicate that net use among women of reproductive age (an indication of use by pregnant women) remains very low, which means that IPT could yet play a significant role in national malaria control strategies. As countries accelerate efforts to control malaria during pregnancy, coverage is expected to increase.[43]

Prevention

Apart from the efforts of MMV and others to create new and improved drugs to treat malaria, there are several well-established public health approaches for its prevention. Addressing the problem from an ecological standpoint, the US National Institute of Allergy and Infectious Diseases (NIAID) grantees are studying the relationship between vegetation and mosquito abundance in Belize and mosquito behaviour and larval ecology in Kenya; the effect of rice irrigation on malaria prevalence in Mali; and how mining and deforestation are leading to the emergence of important new malaria vectors in Brazil.[44]

Impregnated bed nets and other materials are treated with pyrethroids, a synthetic derivative of pyrethrum extracted from dried chrysanthemum that acts as a nerve poison for insects. The ***insecticide treated bednet (ITN)***, first studied in The Gambia, was shown to reduce overall childhood mortality by 60% when combined with malaria chemoprophylaxis. Even when used alone, studies have shown that ITNs reduce mortality by 16% to 33%, depending on the transmission pressure. Pyrethroids are the only insecticides that have reached the market for vector control in the past two decades and it they are currently the only group of insecticides recommended for treating mosquito nets.[45] Several governments, including the Philippines, Solomon Islands and Vanuatu have initiated ITN promotion as one of their main malaria control objectives. Very successful government-financed ITN programmes today are found in China and Vietnam, where the public sector's chief contribution is to offer regular net re-treatment services. In contrast to the situation in Asia, in Africa, where many nets and

insecticides have been provided for free or at a subsidized rate, less than 5 to 20% of nets are re-treated. [46] As an important step towards making ITNs more affordable, African governments in 2000 committed themselves to reducing or eliminating the tariffs and taxes imposed on mosquito nets, netting materials and insecticides, in order to help lower retail prices. Almost 20 countries have reduced or waived such taxes since the Summit. It will be important to ensure that such reductions in tariffs are fully passed on to consumers in the form of lower prices, rather than augmenting the profits of manufacturers.

Increased funding from the Global Fund has boosted the deployment of insecticide treated mosquito nets. By the end of 2004, massive efforts to extend the use of nets will have been undertaken in many countries, notably Eritrea, Togo and parts of Tanzania and Zambia. But despite its proven benefits, current ITN use in sub-Saharan Africa is remains too low. Only 2% of children under 5 years of age slept under treated bednets in 2002, the proportion rising to just 15% for untreated bednets.

One of the challenges in assuring the effective use of ITNs is the requirement for repeated re-treatments every six months. *Breakthroughs have been achieved with the development of long-lasting insecticidal nets, which retain their efficacy for up to five years without re-treatment, and re-treatment packages using a long-lasting insecticide to extend the time needed between re-treatments.* The technology for this development was recently transferred to Tanzania in a collaboration between private and public sector actors. A to Z Textiles now produces about 300 million of these new long-lasting nets each year and hopes to scale up production to one-million in 2005. A to Z Textiles' Olyset, one of two long-acting nets currently approved for use by WHO, is built with fibers containing permethrin, which is slowly released for up to a five-year period. Partners in the Olyset venture include Sumitomo Chemical Company in Japan, which is providing the manufacturing technology, ExxonMobil in the United States, which is supplying chemicals and advice, a non-profit global venture fund in the United States called Acumen Fund, which put up the financing, and several United Nations agencies, including WHO, which monitor quality control and have purchased nets.

Indoor residual insecticide spraying (IRS) started on a large scale in the 1930s with pyrethrum, and then with DDT. Over the last 30 years, however, DDT-based IRS declined, apart from in urban epidemics and refugee camps worldwide and occasional use for the protection of employees and local communities in malaria-endemic areas. While a few countries continue to use DDT, there is a lack of government support and financing and general disapproval of DDT by the international community. Sprays of any kind must be employed circumspectly, on the basis of careful analysis of the local evidence.

An important barrier to both ITNs and IRS use is their dependence on user cooperation, which can in some cases limit the effectiveness of prevention campaigns. Some residents of endemic areas forfeit their benefits by painting or replastering sprayed walls, while other families evade IRS altogether by locking their houses during the spaying round.[47] In addition, there is a common misconception that ITNs are meant to control mosquitoes as opposed to malaria. In urban areas with untreated wastewater and high year round mosquitoes, this misconception favours ITN use. But in rural areas, where there are fewer mosquitoes but year

round biting, ITN usage is rarely sustained. A survey in Kenya highlighted the fact that about 30% of ITNs in homes were unused. Children less than 5 years of age, who are the most at risk, were less likely to use ITNs than older individuals.[48] This underscores the need for health education campaigns and the development of a 'net culture' through promotion and publicity.

Finally, a further challenge exists in that the problem of resistance also applies to insecticides; there is already evidence that anopheline mosquitoes are developing resistance to pyrethroids.[49] Moreover, indoor residual spraying needs to be determined by the resting and feeding habits of the mosquito vector, and knowledge of this requires a capacity to assess and monitor the insect's behaviour.

Vaccines

Human populations residing in malaria endemic areas naturally acquire some level of protective immunity over time. Repeated exposure to malaria by those in highly endemic regions generates a level of clinical immunity in adults and children, but very young children remain highly vulnerable, as do pregnant women who seem to lose their immunity. One approach taken by some groups has therefore been to create a ***vaccine*** targeting these populations. Malaria vaccine research and development is being supported by the US government, primarily by the Walter Reid Army Institute for Research (WRAIR) and Naval Medical Research Center (NMRC), though funding also comes from NIAID, Department of Defense (DoD), USAID, CDC, the Wellcome Trust, WHO, European Commission, the Bill and Melinda Gates Foundation and others.

There is no commercially available vaccine against parasites that infect humans. Not surprisingly, then, the effort to develop prophylactic vaccines is the most technically challenging approach to malaria prevention. Nevertheless, significant progress has been made in the development of a malaria vaccine, though the first licensed product will not be available before 2010 at the earliest. There are multiple candidate malaria vaccines in clinical development, many of which have started, or soon will be, in human clinical trials.[50] Four categories of vaccines are under development:

1) pre-erythrocyte vaccines protect against the infectious form of the disease injected by mosquito by inhibiting it from invading and developing in the liver;
2) erythrocyte or asexual blood stage vaccines stop the parasite from multiplying in red blood cells and being released into the bloodstream;
3) transmission-blocking vaccines target the gametocyte or sexual stage vaccines interruptomg the cycle of transmission by short circuiting the development of the parasites ingested by mosquitoes.
4) combination vaccines which blend one or more of the groups above.

There are currently 16 candidate pre-erythrocytic vaccines, including a candidate (RTS,S/AS02A) being pursued by a partnership among GlaxoSmithKline Biologicals (GSK), PATH's Malaria Vaccine Initiative (MVI) and several African governments (e.g. The Gambia and Mozambique[51]). Fifteen candidate vaccines against the asexual stage of the parasite are in the pipeline, and two candidates are in development against the sexual stage.

However, GSK's RTS,S/AS02A, according to PATH's MVI, represents a major breakthrough, as the first proof of concept that an effective malaria vaccine is technically possible. In African children aged 1 to 4 years old, studies show that a pre-erythrocytic vaccine can reduce *P. Falciparum* infection and malaria disease in the face of high natural exposure. The vaccine has been under clinical development for nearly 20 years. In 2004 it was tested a phase 2b trial in just over two thousand children in Mozambique. Vaccine efficacy against the first clinical episodes was 29.9%, 57.7% against severe malaria, 45% for extending time to first infection.[52] Research on the vaccine continues to evaluate its safety for use in infants, compatibility with other vaccines, and how long its protection lasts. Further trials are underway to better answer these questions. Nonetheless, it is widely believed that even a moderately effective vaccine could have an enormous impact on the sub-populations at risk.

A different approach to vaccine development is being employed by one group of researchers in the United States, which is using a form of *P. falciparum* that has been weakened by radiation. A vaccine based on this method is on its way into clinical trials, and will be manufactured by a US company, Sanaria, and with funding from the Gates Foundation through OneWorld Health, and the US Army.[53] [54]

All but one commercially available vaccine are constructed from whole viruses or bacteria or their components. The single exception is a recombinant protein vaccine against hepatitis B, and it is this vaccine upon which the GSK malaria vaccine is based. Today, many vaccine candidates are based on individual components created in labs using recombinant products. Because of the complexity of the malaria parasite and its life cycle, a heightened immune response that mobilizes both antibodies and the body's killer T-cells in an attack against multiple proteins at different stages of the life cycle, may well be required to create a highly effective (versus moderately effective) vaccine. And, if this is the case, then it presents a technical challenge that has never before been solved.

2. DIABETES

There are two principal forms of diabetes[55]:

- **Type 1 diabetes,** or insulin-dependent diabetes, is a severe deficiency of insulin due to the destruction of insulin-secreting islet cells in the pancreas by the body's own immune system. This makes type I diabetes an autoimmune (or "against itself") disease. It is seen more often in younger people, and in 90% of cases there is no obvious family history. Specific events, such as certain infections, can trigger underlying genes that lead to the condition.

- **Type 2 diabetes**, or non-insulin-dependent diabetes, occurs when insulin levels are inadequate or the insulin does not work properly, often because of ineffective release of insulin (i.e. not enough is made) combined with ineffectiveness at the site of action (i.e. insulin resistance). Type 2 is much more common than Type 1, accounting for about 90% of all diabetes cases worldwide. It occurs more frequently in adults, but is being noted increasingly in adolescents and children. A significant proportion of individuals with this form of diabetes are overweight or obese, and obesity itself causes or aggravates insulin resistance. Type 2 diabetes is strongly familial but it is only recently that some genes have been consistently associated with increased risk for the disease.

A form of the disease, gestational diabetes, is first diagnosed during pregnancy and occurs when there is glucose intolerance during pregnancy. Afterwards, women often return to a normal metabolic state. Hormones secreted by the placenta block the action of the woman's insulin in her own body. The woman's excess blood sugar flows back through the placenta, giving the fetus high blood glucose levels, which causes its pancreas to make extra insulin to get rid of the blood glucose. Babies with excess insulin become children who are at risk for obesity and adults who are at risk for type 2 diabetes.

BOX 4. Obesity Among the Poor

There is a myth that obesity is a problem of the over-indulged rich. In fact, it affects a growing number of poor. Many developing countries are undergoing a rapid demographic and nutritional transitions, and have witnessed an increasing level obesity among the poor, particularly those in urban areas. In contrast to middle income countries, obesity tends to decline as income increases, especially among women. Changes in diet and increased inactivity work together to drive overweight and obesity. These trends are most marked among low income groups, who improve their income and buy high fat/high carbohydrate energy-dense foods, to the detriment of grains, fruits and vegetables.

Uauy et al, J Nutr 2001; 131(3):893S-899S

Diabetes is a multifactorial disease, caused by a complex interplay of genes and environmental factors that together lead to the abnormal regulation of glucose owing to problems with the hormone insulin. Most types of diabetes are polygenic, which means that susceptibility depends on inheriting several abnormal genes affecting various characteristics, such as the number of insulin-producing cells in the pancreas, how insulin is secreted and its activity, autoimmunity (where the cells of the immune system attack normal cells in the body), and fat distribution.

In diabetes, the pancreas is not doing an adequate job of producing insulin, or when the insulin it produces is ineffective. Such deficiency can be inherited or acquired, and results in an increased concentration of glucose in the blood. High blood glucose levels damage many of the body's systems, in particular the blood vessels and nerves. Figures from the United States show that diabetes lowers life expectancy by up to fifteen years, increases cardiovascular disease risk two- to four-fold, and is the main cause of kidney failure, lower limb amputations and adult-onset blindness.[56] A very disturbing feature of diabetes has been its clustering with other well-known cardiovascular risk factors. The frequency of obesity, hypertension and elevated blood lipids are dramatically increased in persons with diabetes; the collection of risk factors, has been called the *deadly quartet*, the *metabolic syndrome*, *syndrome X*, and *insulin resistance syndrome*. In relation to infectious disease, one study has noted that there is an increased incidence of multi-drug resistant tuberculosis (TB) in diabetic patients and the risk that TB infection progresses to disease status is three times higher in diabetic patients.[57]

One hypothesized factor that increases the risk of developing type 2 (non-insulin-dependent) diabetes is the programming of glucose and insulin metabolism during fetal life by influences that also affect fetal growth, such as maternal nutrition, the nutrient supply line to the fetus, or alterations in endocrine function.[58] In addition to the relationship between overweight or obesity and type 2 diabetes, one systematic review[59] suggests a correlation between low birth weight and type 2 diabetes. Because poverty is strongly associated with low birth weight, the latter evidence points to an unexpected risk factor for type 2 diabetes for infants that survive the numerous other conditions threatening their health due low birth weight. A second study, by Levitt et al (2000), revealed that impaired glucose tolerance and elevated blood pressure can occur in low birth weight, non-obese, young South African adults.[60,61]

In 2030, China and India will be home to the largest number of people with diabetes.[62] They characterize countries that increasingly face the "double burden" of disease, which combines high mortality rates from infectious diseases and high risk of developing debilitating chronic conditions. Already India, where 2.5 million children still die from infections like pneumonia, diarrhoea and malaria each year, has the highest number of people with diabetes in the world. In South Africa, 28% of deaths are due to infectious diseases and 25% are due to chronic noncommunicable diseases.[63]

Prevalence figures indicate that globally, while the number of people with type 2 diabetes is today a major problem for many developing countries, type 1 diabetes is principally an affliction of North Americans and Europeans. While the numbers for type 1 are growing by 3% per year worldwide, they still remain markedly lower in developing countries. Low numbers are at least in part due to the dearth of available prevalence data for sub-Saharan Africa. Existing prevalence data distributions might also be explained by differing genetic or hereditary factors in populations. But low prevalence rates could also suggest a divergence because persons with type 1 diabetes do not live long enough to be counted in epidemiological surveys, or because of confusion about symptoms. In sub-Saharan Africa, where infectious diseases are a major public health concern, coma may be mistaken for cerebral malaria and the wasting that accompanies poorly controlled diabetes may be confused with HIV/AIDS. Moreover, individuals with type 1 diabetes, who often develop the

disease as children or adolescents, will not survive more than a matter of months, without access to insulin.

Economic and Social Impact

Diabetes is a devastating disease for the poor, because its management calls for a careful daily regimen of diet and exercise and, in the case of type 1, multiple injections with insulin. For a family in the United States with a diabetic child, 10% of family income goes towards diabetes care. This financial burden is more pronounced in poorer countries, where treatment represents 20-25% of family income, especially for families without access to subsidized care.[64] Calculations for one African country show that insulin costs US$156 per person annually, or about two thirds of total outpatient health care costs for type 1 diabetes.[65] Effective management of insulin-dependent diabetes requires regular monitoring of blood glucose levels, using a glucometer or urine strips, so that individuals can assess their body's response to different doses, eating or exercise patterns. Even using the best treatments available today, people with diabetes are unable to mimic normal control of glucose levels. Extremely low blood glucose levels, or hypoglycaemia, can lead to coma; very high blood glucose levels, or hyperglycaemia, can lead to increased risk of developing complications in the longer-term. For people with diabetes living in poor settings where eating one meal a day can be a luxury, the challenges are enormous.

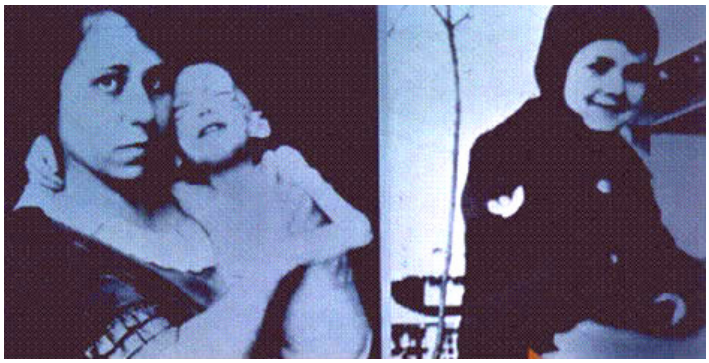


Figure 1. A child before and 32 days after the first injection of insulin in 1922. *Source: Insulin For Life (www.insulinforlife.org)*

Direct costs to the healthcare sector include hospital services, physician services, laboratory tests and the daily management of diabetes, which includes the procurement, storage and distribution of products such as insulin, syringes, oral agents to control glucose levels and blood-testing equipment. For most countries, the largest single item of diabetes expenditure is hospital admission for the treatment of long-term complications, such as heart disease and stroke, kidney failure and foot problems. Many of these complications are preventable with prompt diagnosis of diabetes, effective patient and professional education and comprehensive long-term care.

In wealthier countries, it is often the case that minorities bear an excessive burden of diabetes. For instance, in the United States, diabetes and its complications disproportionately affect African Americans and Hispanics: nearly 12% of the former and 14% of the latter are affected by diabetes, almost double the prevalence among Americans of European descent.[66] Aboriginal populations around the world also tend to have very high prevalence of diabetes, attributable to both lifestyle and genetic factors.[67]

Summary of major Achievements and Challenges

Treatment

In 1921, two Canadian researchers revolutionized care for diabetes when they discovered the effectiveness of insulin in treating the disease. Prior to their discovery, people with diabetes faced a slow but inexorable march towards death, with constant thirst and a voracious appetite. Because they were unable to process their food, they would waste away. Around the time of the discovery of insulin, diabetes was managed through a low-carbohydrate and sugar diet high in fat and protein, which allowed people with diabetes to live for a few additional years, at most. Today, the availability of insulin has transformed the lives of people with diabetes who can access it, making it possible for people to live a relatively normal life with diabetes. Survival rates are improving, as a result of better insulin formulations and delivery, as well as improved methods for monitoring glucose control. According to one type 1 diabetes registry, death rates dropped by more than 50% for those diagnosed between 1975 and 1979 compared to those diagnosed 10 years earlier.[68]

But although insulin has unquestionably brought enormous benefits to patients, today the control of insulin-dependent diabetes using available products requires a burdensome daily regimen of multiple injections, careful attention to diet and physical activity, and regular monitoring of blood glucose. In the case of type 2 diabetes, individuals often need to take several different types of medication, to help to regulate their blood glucose levels and to prevent the onset of complications. Even the most motivated and well-informed people with diabetes rarely achieve the level of control of blood glucose levels to prevent the development of later disability and disease. For low income groups, there remain enormous barriers to accessing adequate supplies of insulin, the supplies needed to make adequate administration of insulin possible, such as needles and syringes, as well as urine strips or other means of monitoring glucose levels. Lack of financial resources combine with a lack of understanding of the disease, to make adhering to the recommended regimen nearly impossible for the poorer segments of society. As noted earlier, because of ethnic, nutritional and other factors, it is often minorities even within wealthy societies who are most susceptible to developing diabetes and its complications.

For both types 1 and 2 of diabetes, complex genetic and environmental factors act together in the development of the disease. A large number of genes is involved to varying degrees in the etiology of diabetes, making it a very difficult task to tease out their respective roles. For instance, 18 different chromosomes have shown some positive evidence of linkage to the disease.[69] A second important risk factor is the presence of antibodies directed against the insulin-producing beta-cells in the pancreas. Moreover, different racial and ethnic groups often express distinct genetic polymorphisms that interact to make them susceptible to developing type 2 diabetes, suggesting that large samples are needed from many different groups to identify key genetic determinants of diabetes -- a process that is essential to understanding the cause and mechanisms of diabetes, and in identifying new targets for drug development. What this suggests is not that progress is impossible, but that a breakthrough in our understanding of the disease is still many years down the road.

All the same, researchers now know that one family of genes implicated in the body's immune response is responsible for nearly half of the genetic risk for type 1 diabetes. This could make it possible to identify those at highest risk of developing diabetes before they present with life-threatening metabolic problems. About 85-90 percent of people with type 1 diabetes have HLA genotypes known as DR3 and 4, and people with those genotypes are more likely to develop type 1 diabetes. Such knowledge has provided a basis for clinical trials now being planned to assess methods to prevent type 1 diabetes and to treat it in recently diagnosed patients, as well as to identify novel therapies.[70] Several genes have also been identified that predispose people to type 2 diabetes, including so-called susceptibility genes which may contribute in a small way, such as the gene for insulin itself (the IDDM2 gene on chromosome 11) and the genes that regulate its secretion. But having these "diabetic" genes is not an inevitable ticket to illness; some people will not go on to develop diabetes in spite of "genetic risk", especially if they strictly control their diet and weight (putting less demands on the insulin producing cells) and keep active.

Because diabetes afflicts a large and growing number of individuals in wealthy countries, there are considerable commercial incentives for the private sector's involvement. The total market for diabetes products totalled US$12 billion in 2002[71], and about twenty companies, including major pharmaceutical firms, are engaged in R&D for diabetes treatments. Six of these companies (Eli Lilly, Takeka Novo Nordisk, GSK, Bristol-Myers Squibb and Aventis) account for 75% of global sales.[72] The NIH provides considerable funding for diabetes research -- the most in the world -- and diabetes was made a priority by the European Commission in its Sixth Framework Programme to fund research across the EU.[73] There is no doubt that important advances have been made because of the activities of these players, independently and through various consortia. Research has been focused around several key areas, including improved treatment methods and delivery systems, the genetics of the disease, and possible cures.

A search of the on-line database of NIH-sponsored clinical trials[74] using the search term "diabetes" brought up 231 clinical studies. A considerable proportion of all late stage (Phase 2 or later) research is carried out in ***oral antipeople with diabetes*** and other drugs for diabetes, which delay or treat symptoms of diabetic complications. There are several sub-classes of oral antipeople with diabetes; among them, alpha glucosidase inhibitors are relatively well-established, and the main biguanide, metformin, first synthesized in 1922, is now produced in generic form.[75] Many types of ***insulin*** are on the market, which is important because each diabetic needs a tailored combination to approximate the body's normal pattern of secretion. ***Insulin pumps*** have also been created, which deliver micro-droplets of insulin continuously into the body. They are used in some type 1 diabetes patients to achieve strict control of blood glucose, and have been shown to reduce the frequency of hypoglycaemia compared to intensive injection therapy. At the same time, some of the large pharmaceutical companies are continuing to focus their research into developing more sophisticated and less invasive blood glucose monitoring techniques. The consultancy group IMS notes that "in developing countries, considerable growth can be expected in the core markets for oral antipeople with diabetes and insulins, as the epidemic gains momentum. However, marketers will need to balance their investment in these markets, in the light of the large volume growth that can be expected to come from low-priced generics and local brands". The prospect of lower costs

through increased competition among generics is welcome, particularly for people with diabetes in poorer countries, who in most cases must pay for their medication out-of-pocket.

Progress has been made in the development of drugs to prevent the complications of diabetes. Nerve growth agonists have been used to treat neuropathies, as well as a new generation of statins for the rigorous control of lipids; the latter class of drugs has proven highly effective in protecting against cardiovascular disease among people with diabetes. There are also signs the possibility of making fixed dose combinations for cross risk factors (e.g "polypill"). A recently published paper outlines a strategy to combine aspirin, a statin, three anti-hypertensive drugs and folic acid in one pill for patients with vascular disease and those over the age of 55 years, which could, according to the authors, reduce deaths from heart disease and stroke by 80%.[76] Because versions of all the drugs are now off patent, the pill could theoretically be produced at very low cost (although costly clinical trials may be necessary). Despite some optimism, there is concern about the practical and political feasibility of making and marketing such a pill, as well as the extent to which it could address patients' specific needs.

Pancreatic transplantation was first used for the treatment of type 1 diabetes in humans in 1966.[77] In that early era, the rates of graft and patient survival were low, so very few procedures were performed until 1978. Improved surgical procedures as well as better immunosuppressive regimens explain how, by the end of 1997, nearly 10 000 pancreatic transplantations had been recorded in the International Pancreas Transplant Registry. The results from different centres vary depending on operative experience and patient selection. The 1-year rate of graft survival[78] was 82% when a pancreas and a kidney were transplanted simultaneously (SPK), 71% when a pancreas was transplanted after kidney transplantation (PAK), and 62% when a pancreas was transplanted alone (PTA). Due to the limited number of available donated organs, scientists are beginning to search for alternative organ sources. One possibility is xenotransplantation, or the transplant of an organ (or tissues or cells, in the case of diabetes) from one species to another. Another strategy involves the genetic engineering of animal islets to make them less likely to succumb to immune system attack and destruction. If successful, these "super islets" would then go into the next phase of testing, pre-clinical testing in larger models, in the shortest time possible.

Another area of research that has generated some promise is transplantation of ***insulin-producing islet-cells***. This is the biological replacement strategy that attempts to give back to type 1 diabetic patients the pancreas cells (islets) that have been destroyed by their own immune system. A landmark study was performed in Canada in 2003, in which seven patients received transplants, and remained insulin-free for up to fourteen months. Over 40 Canadian patients have now been treated at the University of Alberta, and 82% of them maintained independence from insulin at the 1-year mark. However, while islet transplantation is becoming more successful as a potential treatment for this disease, the premature death of transplanted cells is still a problem that needs to be solved. Gene therapy research projects at the Diabetes Research Institute, part of the University of Miami, seek to reduce the number of islet cells that die after transplantation by genetically modifying them before transplant so they are not rejected by the recipient. The overall goal is to improve islet survival and reduce the number of cells needed per transplant. This is especially important since the number of

organs available for transplant is so small compared to the increasingly large number of patients who could benefit from this therapy. For an average-size person (70 kg), a typical transplant requires about 1 million islets, extracted from two donor pancreases. The potential success of this approach is thus constrained by the shortage of available donor pancreases, in addition to technical hurdles as well as considerable treatment costs mounting to $70 000 for the transplant and $30 000 for antirejection medications in the first year.

Several important studies have provided proof of principle of the ability of ***stem cells*** to transform into any type of cell, illustrating their potential to form the basis for critically-needed medical therapies for type 1 diabetes. For a stem cell to become an islet cell, the cell must create a series of proteins in a specific sequence. In the last decade, scientists have developed a good understanding of the sequence, but they have not yet learned to prompt the cell to create the essential proteins. In 2003, the John P. Robarts Research Institute in Canada reported that transplanted adult stem cells derived from bone marrow can induce the recipient's pancreatic tissue to repair itself, restoring normal insulin production and reversing symptoms associated with diabetes in animal models of diabetes. In 2005, the Diabetes Research Institute discovered a shortcut for turning embryonic stem cells into the insulin-producing cells destroyed by Type-1 diabetes. The study was done with mouse stem cells. The next step, already underway, is to try similar experiments on human cells.

A considerable proportion of the world's people with diabetes, who live in varying degrees of poverty, have not yet experienced the benefits of insulin's discovery in 1921. Improving access and availability within these populations, given major shortcomings in infrastructure and knowledge at all levels, is a tremendous challenge. Advances in the development of new products to treat diabetes are good news -- but there is little to suggest that they will be any more accessible or affordable for low income groups. A number of groups are working to improve access to insulin and supplies, and while important, their work operates on a relatively small scale. Some organizations of note, such as the World Health Organization, the World Diabetes Foundation, the International Diabetes Federation, and Insulin for Life, have made improving care for diabetes in developing countries part of their mission. A major part of the work to ensure improved access by the poor for diabetes treatments and supplies is a question of educating decision makers about the existence of the disease within their populations, and its debilitating impact on their citizens and on their economies.

For many poor countries, which are still struggling with the scourge of infectious disease, noncommunicable conditions such as diabetes, cardiovascular disease and obesity are not high among health priorities. Scare resources and the devastating, highly visible impact of infectious illness make it difficult to focus funds and attention on other conditions, particularly those requiring complex and long-term care. On the whole, health systems in these countries are ill-equipped to deal with chronic diseases. Countries like India, facing a double burden of both infectious and chronic non-communicable diseases, confront enormous challenges in managing these conditions. But life-saving insulin exists, and is on WHO Model List of Essential Medicines.[79] A great deal more is required to make it available for the poor.

Prevention

Pre-diabetes is a condition that increases the risk of developing type 2 diabetes and cardiovascular disease. There is now strong evidence that type 2 diabetes can be prevented among these individuals through modest changes in ***diet and exercise***.[80] Because obesity is a major risk factor for type 2 diabetes, and is itself a cause for increased insulin-resistance, curbing or preventing excessive weight gain through changes in lifestyle and behaviour can have a major impact on reducing individual's risk. For instance, studies in the United States and Finland showed a reduction of 58% in the risk of developing diabetes among patients who modified their diet and exercise patterns.[81,82]

The major progress that has been achieved is principally in our knowledge about what is needed to prevent type 2 diabetes. Certainly, some individuals have benefited, but large-scale success with prevention programmes has remained elusive. In the case of type 1 diabetes, tools for prevention do not exist, because scientists do not yet adequately understand the factors, genetic and environmental, and their relative contribution to the development of the disease.

The destruction of the insulin-producing function of the pancreas occurs gradually in type 1 diabetes. The possibility of preventing beta-cell destruction in the relatively early stages of the disease progressing is being tested using an ***insulin vaccine*** (an inactive form of insulin), designed to protect against the immune system's attack on the pancreas at the onset of diabetes. The NIH is funding such a study, which is in Phase I trials.[83]

Due to the emerging public concern at the enormity of the impending diabetes pandemic, disease-specific public research initiatives have been put into operation. A large part of the research is undertaken by pharmaceutical companies in the private sector, both independently and in alliance with public institutions and foundations. The NIH of the United States and the European Union coordinate and support most international research in the public sector.

3. *ROTAVIRUS*

Rotavirus is the commonest diarrhoeal pathogen in children. Highly contagious, the disease hits hard and fast: within 18 to 24 hours of exposure, children develop fever, violent vomiting and diarrhoea that, if left untreated, can quickly lead to death. In severe cases, the only recourse is intravenous (IV) fluids. Though its principal means of transmission is fecal-oral, it is also thought to spread through respiratory secretions, person-to-person contact, and because the virus is stable in the environment, transmission can occur through ingestion of contaminated water or food and contact with contaminated surfaces. In contrast to some other diarrhoeal infections, it is not believed that progress in the treatment and control of rotavirus will be achieved by improved sanitation and environmental conditions. This is because of high rates of infection in the first three years of life regardless of sanitary conditions, as well as the failure to document fecal-oral transmission in several outbreaks, and the dramatic spread of rotavirus over large geographic areas during the winter.[84]

For people with a healthy immune system, rotavirus gastroenteritis is a self-limiting illness, lasting for only a few days because the virus is eventually washed out of the system. About one in 40 children with rotavirus gastroenteritis will require hospitalization for intravenous fluids. Immunity after infection is incomplete, but repeat infections tend to be less severe than the original infection. In poor countries, however, where children may be under- or malnourished, suffer from multiple gastrointestinal infections, and lack ready access to a hospital, the virus is far more deadly.

Though it has perhaps been around along as humans, rotavirus is a relatively "new" disease, having only been discovered clinically in 1973. And it has taken many years to get a sound estimate of the disease burden. In 1982, Snyder and Merson published their landmark article giving the first estimate of global morbidity and mortality from diarrhoeal disease based on active surveillance data collected from longitudinal studies of children.[85] During the intervening decade, diarrhoeal disease control programmes have been established in many countries, with oral rehydration therapy (ORT) as the keystone, and new methods have been developed for assessing mortality.[86] Between 1983 and 1990, the number of national programmes against diarrhoeal diseases rose from 35 to 80.

Economic and Social Impact

Rotavirus is ubiquitous but its toll varies enormously. In the United States, rotavirus gastroenteritis causes an estimated 70 000 or more hospitalizations a year, half a million doctor and clinic visits, and 20 to 40 deaths (or 2% of childhood deaths). By contrast, in developing countries about 1500 children die each day of rotavirus infection. By age five years, almost all children will have had an episode of rotavirus illness and one in 293 will die.[87] Eighty-two percent of rotavirus deaths occur in the world's poorest countries.

Paradoxically, in some countries diarrhoea is so common that it is not perceived as important for policymakers. This speaks to the need of maintaining a strong evidence base about the prevalence of rotavirus, as well as the impact of intervention strategies for its control and management. WHO is now investigating the benefits of audience research -- a strategy for gathering information about the attitudes, knowledge, interests, preferences or behaviours of

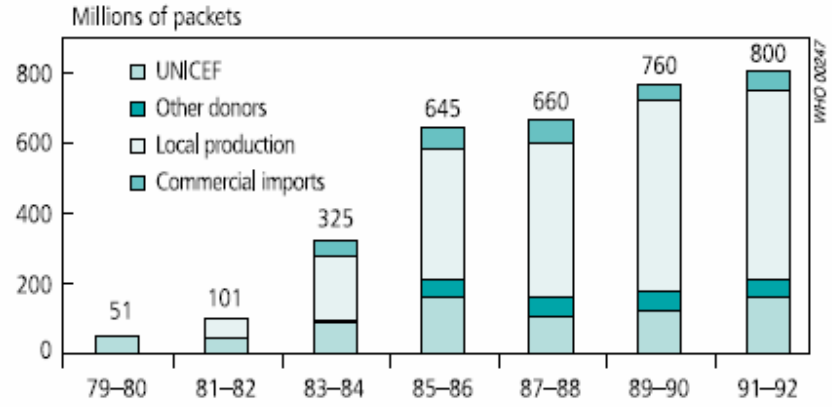
specific segments of the target audience -- in order to improve the effectiveness of communication, design and uptake of vaccines in countries.[88] The basic idea is to do better at tailoring vaccine programmes to the expectations of end-users, as it were.

Summary of Major Achievements and Challenges

Treatment

Oral rehydration salts or **ORS**, a simple home remedy that combines water, salts and glucose in specific proportions, was developed in 1968 by researchers in Calcutta and Dhaka as treatment for cholera. In 1978, ORS was described by an editorial in *The Lancet* as "potentially the most important medical advance of this century".[89] The solution was found to be the best way to rehydrate a child suffering from diarrhoea (including diarrhoea due to rotavirus infection), and became the cornerstone of oral rehydration therapy (ORT), which over the years has come to emphasize the need for lots of fluids and continued feeding during diarrhoeal episodes (UNICEF).[9091]

Fig. 1. **ORS supply in developing countries, 1979–92**



Before ORS, treating dehydration by giving children water to drink was ineffective because the liquid ran through the digestive tract too quickly to be absorbed by the body. Using an IV drip bypasses the digestive system, but it is an invasive and traumatic procedure for children, and requires medical professionals who are typically unavailable to a great number of affected families. Adding substances like glucose (or molasses) and salt to water in certain proportions allows the body to absorb the liquid through the intestine.[92]

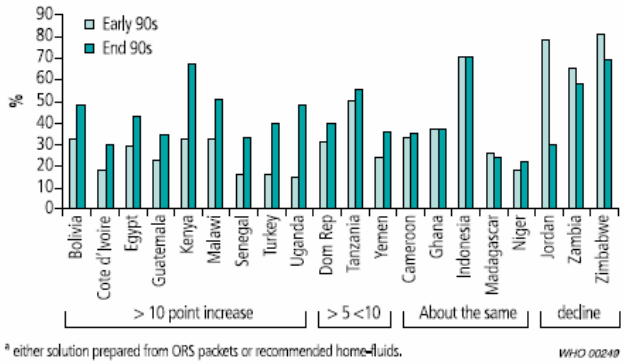
ORT has had a dramatic global impact. It is now given to the majority of children with diarrhoea, in developing and developed countries. Under-five deaths by diarrhoea have dropped from an estimated 4.6 million per year in 1980 to about 1.5 million in 2000. Deaths attributable to diarrhoea declined in both global estimates and country estimates: annual under-five deaths were one-third of their 1980 value in 2000 and less than one half of their 1990 value, meeting the goal established in 1990 at the World Summit for Children of reducing diarrhoea mortality by half. According to some authors, "Despite…limitations the management of diarrhoea is possibly second only to immunization coverage as the best documented indicator related to health services for children" (Victora et al, 2000). But while deaths due to diarrhoeal infection have declined markedly, especially among children under 1 year, morbidity levels remain high.[93]

According to UNICEF,

> Diarrhoea was estimated to be the number one killer of children under five at the beginning of the decade. By 2000, the goal had been achieved with diarrhoea-related deaths declining by half. It is estimated that more than 1 million deaths may have been prevented every year. Success can be attributed to the promotion and use of oral rehydration therapy.[94]

The up-shot of the advent of this therapy can be characterized in four ways: the adoption of ORT as the primary therapy for acute dehydrating diarrhoea, the establishment of national ORT programmes, scientific knowledge gained from studies into intestinal absorption of oral rehydration solutions, and the implications or ORT for the next decade. Better scientific understanding of the intestinal absorption of ORT has led to the development of new formulations that enhance absorption of nutrients and repletion of electrolytes[95].

Fig. 3. **Change in % of children with diarrhoea that received ORT[a] during 1990s for selected countries**



[a] either solution prepared from ORS packets or recommended home-fluids.

WHO 00249

Rehydration may be carried out either by the oral or intravenous route depending on the degree of dehydration. In severe cases, where rapid dehydration occurs, ORT is insufficient and urgent medical intervention is required. Unfortunately, parents and caregivers often stop administering oral rehydration solution when there is vomiting, which is of predominant in children with rotavirus infection.

An estimated ORT coverage of 40% in developing countries was achieved during 1993, which represents a considerable improvement over the coverage rates of close to zero in the 1980's.[96] There is evidence to show that a failure to engage in the ongoing promotion of ORT can lead to its diminished use. In spite of the dramatic fall in mortality rates and overall improvement in outcomes, it remains critical that the dissemination of information, ORS packets and support to communities continue.

With advances in scientific understanding of diarrhoeal disease, the cornerstone of treatment remains proper oral rehydration -- but rates at which it is used are still disappointingly low.[97] The United States is one example. Though costs are almost ten-fold greater to treat dehydration with intravenous (IV) drip in the hospital than to administer ORS, IV remains more widespread. It has also been claimed that, because of its simplicity, there is still some opposition from the medical establishment to ORT, and a preference for more standard 'medical' interventions.[98] On the whole, however, the move to mainstream ORT treatment has been largely viewed as a success. This being said, it has been pointed out that more attention needs to be given to equity issues because, as the overall mortality rate is reduced, in-country differences will become more apparent. As an example, between 1985 and 1987,

infants in the northern part of Brazil were 5.2 more likely to die of diarrhoea than those in the southern part of the country, a ratio that increased to 8.5 in 1995-97. [99]

Table 3. **Estimates for use rate of oral rehydration therapy (oral rehydration salt solution and/or recommended home fluids), 1993[a] and 2000[a]**

Region	Estimates of oral rehydration therapy use rate (%) by year of publication	
	1993	2000
Sub-Saharan Africa	43	64
Middle East and North Africa	51	60
South Asia	19	69
East Asia and Pacific	49	81
Latin America and Caribbean	58	58
Developing countries	40	69

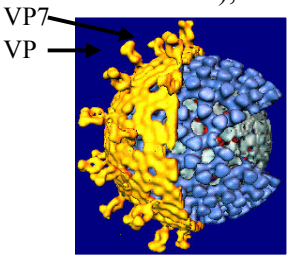
Source: UNICEF's *The state of the world's children.*

[a] Year of publication; average age of statistics usually 3–5 years.

The main application of drugs in the control of rotavirus is in the treatment of selected cases in order to reduce the duration and severity of illness and prevent death.[100] Despite dramatic progresses in the understanding of the pathophysiology of diarrhoea, the list of available and effective drugs to treat rotavirus is indeed short. Recently, however, several new options have appeared that may bear a great potential for the future.

Probiotics -- living microorganisms that can provide health benefit to the host upon their ingestion, beyond the benefits of basic nutrition -- have been used with some benefit in the prevention and treatment of some gastrointestinal disorders, most notably rotavirus-induced diarrhoea in infants and children. *Lactobacillus GG*, a normal inhabitant of the human intestine, has been demonstrated to increase levels of circulating immunoglobulin A (IgA) in infants affected with rotavirus, and has been correlated with a shortened duration of rotavirus-induced diarrhoea.[101] *Lactobacillus GG* has also be reported to be useful as a prophylaxis of diarrhoea in undernourished children, especially those who are not breastfed.[102] But despite evidence of their effectiveness and safety, the use of probiotics in the treatment of diarrhoea is yet to be recommended, even in developed countries. This may be because of perceived shortcomings in design and analysis and the relatively small number of patients studied, which suggests a need for additional large studies.[103]

A new development in treating diarrhoeal disease using standard drugs is ***acetorphan*** (or ***racecadotril***), which inhibits an enzyme called enkephalinase, appeares to be effective in reducing almost half of the stool output of children with acute diarrhoea, including rotavirus. It has been recommended by the Canadian Pediatric Society as both safe and effective for use in children. Its usefulness in developing countries is unclear.



Vaccines

Rotavirus is a triple layered virus particle, whose complex structure has implications for the development of a vaccine. There are five common VP7 serotypes in

	Vaccine	Serotype	Concept	Company/ Inventor
Licensed/ Submitted for License	Rotarix	G1 P1A[8]	Monovalent vaccine, symptomatic human rotavirus strain 89-12.	GSK/RL Ward and DI Berstein
	LLR	G10 P[12]	Monovalent vaccine, lamb rotavirus.	Lanzhou Institute of Biological Products, China/Z-S Bai (China, 2000)
	RotaTeq	G1,2,3,4 P1A[8], 5	Pentavalent vaccine, modivied WC3-QV to also contain VP7 gene from human serotype G4	Merck/HF Clark
Phase II & III	WC3-QV	G1,2,3 P1A[8],5	Quadrivalent vaccine, human-bovine reassortants;bovine parent strain (WC3) with 3 VP7 and 1 VP4 genes from human strains.	Merck/HF Clark
	RV3	G3 P2[6]	Monovalent vaccine, human neonatal strain	Biofarm Indonesia/RF Bishop and GL Barnes
Phase I	116E	G9 P[11]	Monovalent vaccine, human neonatal strain	Bharat Biotech India/BK Das and RI Glass
	I321	G10 P[11]	Monovalent vaccine natural human/bovine reassortant	Bharat Biotech India/BK Das and RI Glass
	VP7	G1,2,3,4 P7[5]	Monovalent and qudrivlent vaccine human-bovine reassortants: bovine parent strain (UK) with VP7 genes from human G1, 2, 3 and 4 strains.	-/AZ Kapikian
	VP4	G6 P1A[8]	Monovalent reassortant vaccine: single human VP4 gene in background of bovine strain UK.	-/AZ Kapikian
		G2 P1a[8]	Monovalent reassortant vaccine: two human genes encoding VP4 and VP7, in a background of bovine strain UK.	-/AZ Kapikian

Table 2. Overview of rotavirus vaccines in the pipeline (*Source: Kirkwood and Buttery).*

humans (G1-G4, G9), but 5 others have been identified. Additionally, there is one predominant VP4 genotype P[8], but others are commonly detected (e.g., P4, P6).[104]

As we saw above, rotavirus is a self-limiting infection because the virus eventually is flushed out of the body. The problem, of course, is that while it runs its course, the virus wreaks havoc on the bodies of the children it affects. Those who do survive a first infection, however, generally face reduced incidence and severity of subsequent episodes of rotavirus infection, which suggests that the disease is a candidate for vaccine control.

In January 1997, the WHO and the Centers for Disease Control and Prevention (CDC) hosted a consensus workshop on rotavirus vaccines for developing countries. The goal of the meeting was to develop a list of activities to expedite the introduction of rotavirus vaccines into developing countries. From that meeting, four groups of activities were proposed, including: establishing studies to define rotavirus-associated disease burden and strain

prevalence; conducting trials to address the remaining issues related to the immunogenicity and effectiveness of rotavirus vaccines in developing countries; establishing plans to address issues related to inclusion of vaccines into the Expanded Programme on Immunisation (EPI); and taking steps to address regulatory and supply issues related to the introduction of new vaccines in these settings. Several of these activities have been carried out or are ongoing.

Since 1985, rapid progress has been made in developing and testing several rotavirus vaccine candidates. In August 1998, after development work involving the strong participations of NIH, Wyeth Lederle Vaccines and Pediatrics introduced in the United States the first long-awaited rotavirus vaccine, Rotashield, a tetravalent rhesus-human reassortant rotavirus vaccine (RRV-TV), covering the four most common serotypes of human rotavirus. In clinical trials, RRV-TV conferred 49% to 68% protection against any rotavirus diarrhoea and between 61% and 100% against severe diseases.[105] It was licensed by the US Food and Drug Administration (FDA) on 31 August 1998, and was soon recommended for all infants in the country as part of their routine immunization schedule. Within the first 9 months, more than 600 000 infants received drops of the live vaccine.

By July 1999, the CDC reported a rare but alarming association between the vaccine and a potentially fatal bowel obstruction called intussusception. Based on the results of its investigation, the CDC estimated that for every 10 000 infants vaccinated with Rotashield, 1 or 2 additional cases (above the normal rate of 1 in 2000 to 1 in 3000 affected yearly) would occur of intussusception. Wyeth removed the vaccine from the market and the Advisory Committee on Immunization Practices (ACIP) withdrew its recommendation for Rotashield. This was widely perceived as an important setback for rotavirus vaccine development, and for developing countries where child mortality due to rotavirus infection is high and the incidence of intussusception comparatively low.[106]

Despite this early disappointment, efforts are ongoing to develop other rotavirus vaccines, and several candidates are in clinical trials. In February 2000, WHO convened a meeting of pediatricians and public health leaders from developing countries on the further use of Rotashield. The delegates agreed that the benefit of the vaccine far exceeded the risk, but it was also agreed that it would be politically difficult to introduce a vaccine that had been withdrawn in the United States.[107] Today, six years after its retraction from the U.S. market, the NIH is trying to revive the rotavirus vaccine. The NIH, whose scientists were instrumental in much of the scientific work behind the creation of Rotashield, announced in May 2004 that it had licensed it to another manufacturer, BIOVIRx, which will attempt to sell it again. According to the NIH, the vaccine's first use will likely be abroad, but the company's president said its plan is to meet at the same time with the FDA and with foreign regulators.[108]

An article by individuals working at the CDC argues that the experience with Rotashield provides four important lessons that should be taken into account in the development of the next generation of rotavirus vaccines, and claims that the setbacks of Rotashield have led to several new opportunities for vaccine research[109]:

- Reinvigorating competition
- Unlocking ethical hurdles in clinical trials
- Pursuing parallel testing of vaccines in developing countries
- Encouraging manufacturers in developing countries
- Increasing global awareness of rotavirus and expectations for the vaccine.

One of the companies that has revisited its own efforts in the area of vaccine development for rotavirus is GlaxoSmithKline (GSK), which licensed its new vaccine, Rotarix, in Mexico in January 2005. According to one report, GSK's action represents a new model for vaccine development and launch, by bringing its product first to a poor country and later introducing it in the United States, Europe and Japan.[10]

In many poorer countries, rotavirus infection occurs at a younger age, there is the presence of unusual strains that may not be covered by a vaccine, there is the possibility of interference by other pathogens that attack the gut, there is the generally poorer nutritional status of young children -- all of which can have an important effect on the efficacy of a vaccine. This presents particular challenges not only to the development of a suitable vaccine, but also for its delivery in poor-resource settings. For enteric pathogens like rotavirus, children are confronted through natural exposure to antigens multiple times, and enteric vaccines are just another exposure to these antigens. This means that a rotavirus vaccine should be designed to work in combination with the natural exposure -- and also means that vaccine evaluation will be more difficult. Other challenges include poor immune responses and protection at young ages, high levels of pre-existing antibodies, multiple serotypes, and the limited reactivity of vaccines across epitopes. The good news is that there is considerable drive at the global level among both public and private sector actors to create a rotavirus vaccine for use in developing countries. Rotarix, the first rotavirus vaccine launched in a developing country, represents an important case that deserves being followed closely.

III. DISCUSSION

Malaria, diabetes and rotavirus take an enormous toll on the poor. We have considered in this paper the nature of their impact, as well as efforts to employ various interventions for their control and prevention. The Bill and Melinda Gates Foundation, the largest foundation in the world with an endowment of US$28.8 billion, is facing a dilemma much like the one that we contemplate here. Under United States' law, foundations must use 5 percent of their endowments each year, and the Gates Foundation must decide how these funds might best be spent. According to a recent Editorial in the *Lancet*:

> Everyone wants to get a piece of the Gates' pie and to offer advice about where the money would be best spent…. Should the Foundation's money be invested in basic research into developing new drugs or vaccines? Or should it be used to implement medical interventions that are known to work, but which governments are unable or unwilling to fund, such as vaccines?

It is this question -- that of identifying critical needs and matching them with solutions that are both optimally efficient and equitable, given limited resources -- that has preoccupied us here.

The Commission has been asked to focus on innovation to generate new or improved drugs and other products; the value of new drugs and products depends to a large extent on whether they address existing needs, which are a function of technical and social considerations. For instance, as we have seen, there is a considerable pipeline of products under development for diabetes, a condition that some have claimed will reach "epidemic" proportions by 2025 in both developed and developing countries. But, when considered in the light of populations of greatest concern to the Commission, this research and development in many cases falls far short of the need.

The reason is that new products often remain beyond the reach of the poor because they are ill-suited for use under the conditions that prevail in these settings. The social and economic constraints that impinge on the ability of the poor and marginalized to access these interventions means that, from their point of view, they may as well not exist. In the case of malaria, the global research agenda is strategically focused on "gaps" -- that is, on identified needs among the worst affected by the disease. Nevertheless, for malaria there is still a major debate about how to dispense limited resources to most appropriately address the immense and complex challenge: is the best option to put funds behind the massive scale-up of proven prevention approaches, to subsidize promising research on the development of a vaccine, to invest in ongoing R&D to create the next generation of antimalarial drugs, or to work to create a synthetic and thus much cheaper form of artemisinin? Rotavirus raises quite different concerns. Since the 1970s, there has been broad consensus that the most promising direction is towards the development of a childhood vaccine, and efforts have correspondingly been centred on this task. Today, vaccines against rotavirus do exist; however, there is still a dearth of efficacy data for Africa and Asia, regions facing heavy

mortality. Oral rehydration therapy (ORT), acknowledged as a massive public health success, has made important inroads but it is not a panacea, and despite important technical and social challenges vaccines are seen as the remedy to the remaining gap.

Table 3. Examples of existing interventions, research directions and challenges for malaria, diabetes and rotavirus.

Disease	Cause(s)	Existing Interventions	Global Research / R&D	Key Challenges
Malaria	Parasite (*P. falciparum, P. vivax)*	CQ, SQ ACTs ITNs IRS	Synthetic artemisinin Malaria vaccine Longer-lasting ITNs New pesticides	Decreasing cost of ACTs Scaling up use of ITNs Feeding ongoing pipeline of antimalarials, pesticides Safety and efficacy in pregnant women and infants
Diabetes * Type 1	Genetic (HLA genotypes) Environmental "triggers"	Insulin products Islet-cell / Pancreatic cell transplants Blood glucose monitors Test strips	New insulin delivery systems Glucose control "Polypill" Molecular basis for onset of diabetes	Improving action of injected insulin to more closely resemble its natural function Reduce complexity, cost of administration of insulin, testing of blood sugar Improve understand molecular mechanisms in order to do better at prevention, diagnosis for types 1 and 2 Develop cure using transplant technology
*** Type 2**	Genetic Diet Overweight/ obesity	Chemoprophylaxis Insulin products Increased physical activity Healthy diets		
Rotavirus	Virus (rotavirus)	ORT Preventive vaccine Probiotics Drugs	Ongoing vaccine development New drugs for use in children	Low-cost vaccine effective in poor countries Scaling up / maintaining use levels of ORT

In this section, we will consider what particular questions are raised by the example of these three diseases -- questions that could usefully inform the Commission's work to prepare proposals that address the "creation of new drugs and other products for diseases that disproportionately affect developing countries". We will do this by introducing a framework to assist us in characterizing key challenges in a way that facilitates the next step, namely the identification of possible remedies.

4. THE WAY FORWARD: A FRAMEWORK FOR ANALYSIS

Malaria, diabetes and rotavirus unquestionably have a significant impact on the poor. The reasons for this are diverse, as we have in the chapters above, and relate to the very different causes, manifestations, impact and available treatment options for each condition. In this section, we will examine the features of key interventions for each of these conditions within a framework, borrowed from a human rights approach, [111] which focuses in on four dimensions of the issue: availability, accessibility, acceptability, and quality. 'Availability' requires that health products and services be on hand in *sufficient quantities* within a country. This includes the existence of a needed intervention in the first place. 'Accessibility' requires that all sections of the population, without discrimination, be within physical reach and able to afford them. For simplicity, we focus here on the affordability component of this dimension. 'Acceptability' relates to the degree to which interventions are ethically and culturally appropriate, and 'quality' refers to their scientific and medical appropriateness. Similar models have been used within the context of public health, to assess quality or evaluate the nature of barriers to health services.[112,113]

Such a framework can be useful for analysis by helping to differentiate in a systematic way the various reasons an intervention may fail to adequately benefit the poor. It can also help in identifying and categorizing potential solutions appropriate for the problems that predominate for a given intervention. If, for example, a key challenge relates to availability, then chances are the solution requires measures to scale-up production -- or, if the product does not exist at all, then ways to spur innovation. Improving acceptability may require, for instance, modifying an intervention or product so that it is more suitable for use in a given setting. Or improved social scientific research, disease surveillance or communication campaigns may be best placed to address the underlying problem.

For the purposes of the Commission, such a schema could be a valuable means of facilitating decisions about which categories of problems and solutions it wishes to focus on, and situating these within a wider circle of approaches for mediating the wide range of public health challenges that exist. For instance, the social determinants that underpin the disproportional impact of diseases on the poor are pointed to but are not directly addressed by the framework; rather, the schema suggests how to frame problems and to identify appropriate solutions *given existing social and economic inequalities*. The inequalities themselves, however, are outside of the schema and outside of the scope of what this Commission can address;[114] but this does not mean that these realities are irrelevant. On the contrary, the determinants of health can, through such a framework, inform proposals that take sufficient account of these realities to be meaningful and even practical.

Here we will apply the proposed framework to an analysis of our three diseases. Table 4 provides a schematic illustration of the application of this framework to particular disease-related interventions, linking each dimension of the challenge with possible strategies.

Availability: A key challenge for malaria control with regard to this dimension is, at the global level, poor economies of scale that prevent the production of the best available antimalarial drug, ACT, in sufficient quantities to meet the demand. With regard to ITNs, we know is that coverage is below desirable levels, though this is likely due to factors other than

the sheer quantity of nets. In the case of a malaria vaccine, availability is inadequate for the obvious reason that there does not yet exist a marketable product, though proof-of-concept has been demonstrated.

	Intervention	Availability	Acceptability	Accessibility	Quality
MALARIA	CQ, SQ				
	ITNs				
	ACTs				
	IRS				
DIABETES	Insulin products				
	Islet-cell / Pancreatic cell transplants				
	Insulin supplies				
	Chemoprophylaxis				
	Increased physical activity and healthy diets				
RV	ORS				
	Preventive vaccine				
POSSIBLE STRATEGIES		Innovation for new products Scale up production	Social scientific research Adapt products for use in low-resource settings	Subsidies/ Financing Reduce cost of R&D / production	Clinical testing

Table 4. 4A's: Availability, Acceptability, Accessibility, Quality.

LEGEND:

Minor/No Challenge

Moderate Challenge

Major Challenge

For diabetes control, it is difficult to assess whether there is a sufficient quantity of insulin, in part because we do not yet have an adequate understanding of the true nature of the global demand. This being said, some advocates have claimed that unused insulin, if appropriately collected and distributed, could go a long way towards meeting the global need for type 1 diabetes.[115] The prevention and management of type 2 diabetes focuses on appropriate diet and physical activity, though many people with diabetes rely on medication to assist with the control of glucose levels. Metformin, which helps to regulate blood glucose, is on the WHO Essential Medicines List; though evidence is lacking, it is improbable that it is in short supply given the large number of individuals suffering from diabetes in affluent countries, and wealthy communities within even poorer countries. And if there is presently a shortage,

scale-up of production should not pose undue problems, particularly in view of the fact that Indian companies are producing generic versions of Metformin. Availability of many of the more advanced techniques for treating or preventing diabetes, such as islet cell or pancreas transplants, are importantly limited at present by the number of available donors, which is why cloning of tissues is the ultimate goal to ensure sustainability.

Rotavirus faces the critical limitation that there is no widely available vaccine on the market. Only one rotavirus vaccine is presently on the market in Mexico, although there are plans to register it in many more countries by the end of 2005.[116] Still, at present rotavirus vaccines are not widely accessible to the poor. Moreover, decisions in wealthier markets, where vaccines normally make their debut, often do not take into account relevant factors for developing countries -- like the case of Rotashield -- and this can have a harmful effect on access is poorer markets. ORS, for its part, is nearly ubiquitous in so far as it can be simply prepared in homes. The principal obstacle to availability, then, is awareness and information about its effectiveness and use in treating severe diarrhoea, including diarrhoea due to rotavirus infection. Though it does not address the massive global demand, the introduction of Rotarix into Mexico is an important step, because it breaks with tradition by launching a rotavirus vaccine in a developing countries, where the need is highest.

For both malaria and diabetes, what does not yet exist at all is an adequate, easy-to-use tool for the early diagnosis of the disease. In the case of malaria, self-diagnosis pre-dominates, and for the diabetes (particularly type 1), there is insufficient understanding of its genetic and environmental triggers to anticipate who is at greatest risk. Availability of appropriate diagnostic tools for these diseases is therefore a major issue.

Accessibility: A very prominent challenge for malaria treatment is the relative high cost of ACTs which puts them beyond the reach of the poorest, who are the principal victims of the disease. Intermittent treatment of infants and pregnant women with low-cost CQ and SQ has been shown to work quite well in fending off severe infection, and fits conveniently into existing clinical visit schedules. Problems with resistance in some regions make their widespread use more difficult, and the need to scale up use of ACT more urgent. ITNs and IRS are generally accessible, as low-cost, community-based approaches to protecting high-risk individuals from exposure.

As for diabetes, insulin and its supplies are too costly for low-income families and individuals, particularly in view of the need for a constant supply for type 1 people with diabetes throughout their lifetime. Drugs to regulate blood glucose are similarly out of reach for the economically disadvantaged. And while control of basic diet is a critical component of the management of types 1 and 2 diabetes, this is a major challenge for those who struggle simply to find enough food to survive.

Though one rotavirus vaccine is now on the market in a developing countries, data are still lacking about efficacy in Africa and Asia. The costliness of conducting clinical testing in poorer countries to ensure safety and efficacy is a very real issue for vaccines like rotavirus. ORS is, by contrast, widely accessible because of its simplicity and low cost.

Acceptability: Community-based approaches for the control of malaria like ITNs and IRS have made important inroads, but still face significant challenges in some settings. For instance, increasing the use of nets in some communities has proven very difficult because of widespread preconceptions or misconceptions about their function, and a failure to apply them appropriately to shield the most at-risk groups.

One obstacle to diabetes control relates to the use of needles for the administration of insulin, which are widely seen as invasive and painful. Interestingly, however, the reverse has been witnessed in some areas where the use of needles is viewed as more efficacious and somehow more "medical", and therefore encourages compliance.

The introduction of a new vaccine against rotavirus could present ethical challenges, particularly where there is already a considerable number of childhood vaccines being administered. As we have seen, given the pervasiveness of diarrhoeal infections in some countries, the inability of a rotavirus vaccine to provide overall protection against diarrhoea caused by other agents could lead some parents to lose confidence in vaccines more generally. Additionally, in spite of the longstanding consensus within the international scientific community about the need for a vaccine against rotavirus, there remains controversy in some circles about the added value of focusing attention on the creation yet another childhood vaccine, to the possible detriment of pursuing simpler alternatives (like ORS).

Quality: The main problem *vis à vis* quality for malaria treatment relates to the constant battle against resistance: CQ and SQ, the longtime low cost drugs use largely successfully against the disease, are facing major difficulties as resistance spreads. ACTs have demonstrated a high degree of efficacy, but need to be tested for safety in pregnant women and young children. In time, they too will face the inevitable reality of resistance, and ongoing research is therefore needed to create alternatives.

The arsenal of interventions against diabetes is largely safe and effective, though there may be some risk incurred due to the potential for repeated use of needles in poorer settings. This being said, though unquestionably a life-saving treatment, the effectiveness of insulin is widely viewed to be sub-optimal, requiring a cumbersome regimen and tight monitoring of blood glucose levels -- which increases the complexity and cost of managing the disease, particularly for those with limited resources. Additionally, because insulin is sold in different strengths, each requiring different syringes suitable to accurately measure the units, it is easy to confuse and inappropriately match insulin strength and syringe. This could be particularly problematic, for instance, for countries receiving donations of mixed products.

The rotavirus vaccines currently closest to the market, or on the market, suffer from a lack of data about their effectiveness in the countries where there is the greatest need. In those instances where the data exist, there is evidence that the effectiveness declines markedly in relation to the socioeconomic conditions prevailing in the region.

IV. CONCLUSION

This paper has been rather modest in its aim: rather than propose concrete solutions to the Commission about needed avenues of research, it has sought to focus on a core part of its mandate and to raise some key issues for consideration by the Commission in its own deliberations about proposals. We will briefly summarize these here.

- ***Most diseases*** **disproportionately affect developing countries.** This could sound like a truism, at best, and a vacuous one at worst. In a sense, it is a platitude if one accepts that, almost by definition, the poor and marginalized are more devastated by disease than those who are better off -- particularly if impact is measured relative to others who have access to existing interventions. But for many, it is obvious that the scope of the term "disproportionate" is rightly limited diseases that are found almost exclusively within these developing countries, or in other words neglected diseases (such as malaria), or even to very neglected diseases. While there may be strategic reasons to do this, there are several reasons for accepting an expansive view. First, in a practical sense, the Commission does not give up anything if it accepts an expanded view; it is still addressing neglected (and very neglected) diseases if it addresses the much larger set of conditions that contribute to mortality and morbidity among the poor. Moreover, a broader understanding of what is captured by "disproportionate" takes a more forwarding-looking view, and acknowledges the social, economic and demographic trends that are profoundly affecting the disease burden in developing countries. Epidemiological reports tell us, for instance, that chronic noncommunicable diseases like diabetes will be a major cause of illness and death over the next 25 years, and noncommunicable diseases -- which are already the priencipal cause of death worldwide -- will see their mortality rates increase by more than 15% by 2015.[117] If we consider another vantage point, human rights and equity (as well as standard public health) arguments insist on giving consideration to the underlying determinants of health in the allocation of scarce resources -- including resources for health-related research. This suggests considering the inter-related factors, both social and scientific, that contribute to unequal health. So there are both pragmatic scientific reasons, as well as compelling normative ones, to define "diseases that disproportionately affect developing countries" in such a way that links the suitability of existing products and research pipelines with the ability of poorer populations to enjoy their benefits, rather than in a way that links it narrowly to a particularly set of conditions. In essence, such an approach sees that equity considerations, which apply across diseases, are at the bottom of any disproportionate impact.

- **Improving "access" is not enough.** Part of what the above analysis aims to demonstrate is that "access" alone is an inadequate determiner of the extent to which interventions reach the desired groups. Very often, the term "access" is employed in a manner that can easily confound problems that are of fundamentally different kinds, and impede the application of appropriate remedies. A model which considers the four dimensions of *accessibility, availability, acceptability* and *quality* provides a useful framework for systematically analyzing the nature of the challenges that exist, as well as their possible

solutions. This schema, which is commonly used within human rights analysis to assess the extent to which governments are fulfilling their obligations, frames the problem in a way that could point the Commission to the particular gaps and challenges that exist for different conditions, and to appropriate remedies. In addition, it emphasizes the degree to which vulnerable or poorer groups benefit from interventions. It is therefore one that links products with key features of poverty, and puts the lens on groups of principal interest to the Commission.

- **Interventions should be *available* in sufficient quantities.** In the first place, the right kinds of interventions should exist. If they do not exist, then the principal challenge is to spur the needed innovation to create a product that fills the identified need. Where a suitable intervention already exists but is still unavailable in adequate supply, the question may be solvable through research -- such as by creating a synthetic version of artemisinin, which is produce -- or it chiefly require effective procurement strategies to finance or subsidize the scale-up of production and distribution.

- **Interventions should be *acceptable*, both in terms of their usability and their appropriateness given cultural and other factors.** This requires the right kinds of products, tailored to the specific technical and social needs of the group in question. Knowledge is a critical element of creating acceptable interventions: knowledge of existing gaps in scientific know-how and clinical outcomes, and knowledge of behavioural and cultural norms that prevail within the communities in question. Obtaining this kind of knowledge requires its own kind of research, and relies in many instances on classic epidemiological, social anthropological study. It could also benefit from what today might be termed "social marketing" or "audience research", which focuses on more successful communication strategies, to weave together a picture not only of the scale of the impact of a disease on a community but also of means of more effectively achieving up-take.

- **Interventions should be effective and of good *quality*.** This requires appropriate standards for testing new products, as well as incentives to conduct testing in key populations. There are particular ethical and technical challenges for the testing of products in pregnant women and very young children, particularly those who are poor and marginalized which are often the groups that are most at risk.

- **Interventions should be of reasonable cost to facilitate *access*.** This requires the financing of research, but also the financing of procurement. The first kind of financing drives the direction of research; malaria and rotavirus have greatly benefited from the active involvement of public sector institutions in setting the research agenda for the development of new products. On the other hand, diabetes has not seen intervention from the public sector on the same scale in the research and development end, in terms of targeting research towards the development of products for poorer populations. Financing at the other end of the chain can help with efforts to scale-up access to existing drugs. The IOM proposal for a global subsidy for ACTs, UNICEF's procurement of childhood

vaccines and drugs for decades, and the TB Global Drug Facility present interesting examples of creating financing and centralized procurement for important public health products. The advanced procurement of not-yet-existing products, such as what has been proposed by UK Chancellor Gordon Brown, presents a different model to incentivize R&D in high risk, low-margin areas. Improving the R&D and production process, and therefore making it less expensive to invent and make drugs and other products, can also affect prices, as can reducing tariffs such as in the case of ITNs.

- **Research is a critical part of nearly every phase of the 'discovery to delivery' chain.** Diseases can have a disproportionate impact on developing countries because no effective treatment exists, or because effective treatment exists but is clinically sub-optimal; inadequate supply to implement on a large-scale; too costly to be afforded by low-income groups; less effective, ineffective or of unknown effectiveness in vulnerable groups; inadequate on its own; or impractical for use in low-income settings.[118] Research of various kinds is therefore essential to addressing the impact of these diseases, including to understand better the basic etiology of the disease, to identify possible targets for improved diagnosis / treatment, to create all-new interventions, and to modify existing treatments so that they are effective in sub-optimal settings.

- **'Delivery' concerns should be part of decision-making early in the R&D process.** Malaria, diabetes and rotavirus provide good examples of the role of research across the 'discovery to delivery' chain. The work to develop drugs against malaria has been, for instance, an effort whose work has been driven by the public sector. Because malaria is a disease that mainly affects the very poor, MMV crafted a "wish list" of features that it would target, features that are tailored to meet the needs of those they hoped would benefit from the drug. On the other hand, diabetes research is driven much more by the private sector, which has generated useful products to treat and manage the disease, but which have not been created with an end-user in mind from the developing world. This is not to say that a "wish list" approach is best; it is only to say that the likelihood that a product will be have an impact in a low-income settings is increased if the particular needs, both health-specific and otherwise, are taken account of early in the process. In other words, thinking about the challenges of distribution and delivery needs to start as early in the research chain as possible. It cannot be taken for granted that, once created, a product that shows efficacy under trial conditions will prove effective in the more rugged conditions that characterize many developing countries. Effectiveness is a more relevant measure, and takes into account both intervention's efficacy and its acceptance to those for whom it is intended, under routine conditions.

In concluding, it may be useful to consider the words of Jonathan Mann, well known for his work as a researcher and proponent of human rights within the context of international health:

> The current health and human rights movement is based on a working hypothesis: that the human rights framework provides a more useful approach for analysing and responding to modern public health challenges than any framework thus far available within the biomedical tradition.[119]

It is true that this paper is not about human rights. Rather, it has sought to suggest how the Commission might approach the question of "disproportionate" impact of disease on developing countries in a way that leads to constructive proposals about "new medicines and other products" that can actually address existing dilemmas. That in the process it has recommended the use of a framework often employed for human rights analysis to advance this project suggests agreement with the above quotation: that such an approach is not merely attractive rhetorically, but also highly useful in pointing the way to concrete solutions that address genuine health needs.

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[1] The same metric can be used to assess challenges for diagnostic tests or other classes of interventions. I take it that the list will be sufficiently similar that, for simplicity's sake, the case of treatments suffices.

[2]Resolution of the World Health Assembly, WHA56.27, "Intellectual property rights, innovation and public health," World Health Organization, 2003, http://www.who.int/gb/ebwha/pdf_files/WHA56/ea56r27.pdf (accessed May 24, 2005). (emphasis added)

[3]Here, we adopt the World Bank's definition of a "developing country": Low- and middle-income countries in which most people have a lower standard of living with access to fewer goods and services than do most people in high-income countries. There are currently about 125 developing countries with populations over 1 million; in 1998, their total population was more than 5.0 billion. (Development Education Program Web (DEPweb), "Glossary," The World Bank Group, http://www.worldbank.org/depweb/english/modules/glossary.html (accessed May 24, 2005).)

[4]"Effectiveness" is taken to be a measure both of an intervention's efficacy and its acceptance to those for whom it is intended, under routine conditions.

[5]United Nations Millennium Project, "Investing in Health," United Nations Development Project, 2005, http://www.unmillenniumproject.org/documents/overviewEngHighRes1-23.pdf (accessed on May 24, 2005).

[6]The African Summit on Roll Back Malaria, "The Abuja Declaration and the Plan of Action," World Health Organization, Abuja, 2000, WHO/CDS/RBM/2000.17, http://www.rbm.who.int/docs/abuja_declaration.pdf (accessed on May 24, 2005).

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[19]B. Greenwood and T. Mutabingwa, "Malaria in 2002," *Nature* 6872 (2000), 670-672.
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[21]According to the World Health Organization, there is no direct link to confirm deleterious effects on human health, but there is some evidence that DDT may disrupt reproductive and endocrine function. Given its high efficacy against malaria, the excessive mortality and morbidity caused by the disease, its relatively low cost, and the lack of sustainable alternatives in many endemic countries (as well as the likelihood that ecological contamination is chiefly due to DDT's use as a pesticide, rather the negligible amounts used for public health purposes), WHO still recommends indoor spraying with DDT for malaria vector control. The Stockholm Convention on Persistent Organic Pollutants allows DDT production and use for public health purposes only. However, many donors will not fund campaigns employing DDT. ("Frequently asked questions on DDT use for disease vector control," World Health Organization, 2004, WHO/HTM/RBM/2004.54.)
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[37] World Health Organization, *Report by the Secretariat on Malaria*, 115th Session of EB, Jan 2005, EB115/10.
[38] *Ibid*
[39]United Nations Children's Fund Homepage, United Nations Children's Fund, www.unicef.org (accessed on May 25, 2005).
[40] Roll Back Malaria, "Looking Forward," Roll Back Malaria Partnership Secretariat, 2004.
[41]Mentor Initiative Homepage, Mentor Initiative, www.mentor-initiative.net (accessed on May 25, 2005).
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