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Drug Development: a Perspective from Africa

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Abstract

While Africa accounts for only 10% of the world's population, she suffered 29% of the world's total disease burden and 19% of the deaths in 2000. Over half the deaths were due to infectious and parasitic causes. The development of drugs for some of the major infections is discussed.

A review of the history of antimalarial drugs indicates that these drugs have been developed mainly to protect western army personnel engaged in war in malaria-infested countries. Thus, World War 2 (WWII) was a major stimulus for the discovery of anti-malarial drugs. Similarly, if it had not been for the fact that a large number of American army personnel were infected with filariasis, research leading to the discovery of the first anti-filarial drug would probably not have been done. Furthermore, with the rapid fall in the prevalence of tuberculosis (Tb) in the west, came the lack of interest in the discovery of new anti-Tb drugs, even though Tb remained common in poorer countries. The fact that less than 1% of all the novel drugs that entered the market between 1975 and 1996 addressed tropical diseases continues to emphasise the notion that the health of these countries cannot be left to the vagaries of a profit-driven and market-oriented pharmaceutical industry.

Whenever efficacious drugs have become available, their cost has made them inaccessible to African countries. Limited health budgets have meant that African countries are not ideal markets. Therefore, there is little incentive to invest in drugs that could address prevailing health problems. This way a vicious, self-perpetuating cycle of disease, economic stagnation, poverty, and insecurity is sustained. Getting Africa out of this brutal cycle of disease and poverty is a moral and social imperative. Formation of a global private-public partnership supported by a Global Fund is proposed as a viable option.

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Introduction

This review attempts to reflect on the extent to which drug development is responding to Africa's priority health problems. The World Health Report is now a regular World Health Organisation (WHO) publication that attempts to summarise the health status in 191 member states that are grouped into six WHO regions, namely Africa, the Americas, Eastern Mediterranean, Europe, Southeast Asia and Western Pacific. This grouping provides a convenient way to compare Africa to the rest of the world. The World Health Report 2001 is a summary of estimates for the preceding year[1]. An analysis of the burden of illness in disability-adjusted life years or DALYs (Table 1) indicates that, while Africa accounts for only 10%

Table 1: Burden of disease in disability-adjusted life years by cause in WHO regions, estimate for 2000

Cause	Africa	The Americas	Eastern Mediterranean	Europe	Southeast Asia	Western Pacific
Population (000)	*639,632*	*827,372*	*481,655*	*873,575*	*1,535,634*	*1,687,304*
Infectious & Parasitic Diseases	**182,544**	**12,356**	**31,439**	**6,823**	**86,382**	**20,631**
Tuberculosis	9,788	1,135	2,951	1,603	14,992	5,325
Malaria	35,748	111	1,945	21	1,874	516
Trypanosomiasis	1,558	0	26	0	0	0
Leishmaniasis	395	47	140	6	1,216	9
Lymphatic Filariasis	1,860	9	477	1	2,795	407
Onchocerciasis	879	3	69	0	0	0
Malignant Neoplasm	**6,683**	**10,572**	**3,600**	**17,643**	**15,558**	**24,453**
Neuropsychiatric Disorders	**15,459**	**30,787**	**14,309**	**31,080**	**46,919**	**40,360**
Cardiovascular Diseases	**11,494**	**14,993**	**13,139**	**33,381**	**46,429**	**30,476**

Source: World Health Report 2001, Annex table 3, Burden of disease in disability adjusted life years (DALYs) by cause, sex, and mortality stratum in WHO regions, estimates for 2000, World Health Organization, Geneva
http://www.who.int/whr/2001/en/statistics.htm. DALYs measure the difference between a population's health and a normative goal of living in full health.

of the world population, she suffered over 29% of the world's disease burden and 19% of the world deaths in 2000.

The population pyramids in Africa are characterised by a young population with the majority being aged less than 15 years in most countries. Table 2 displays estimates for death by cause in WHO regions for preventable childhood illnesses (pertussis, measles and tetanus) and other common causes of morbidity and mortality in children such as pneumonia, nutritional deficiencies and diarrhoeal disease. It is clear that more than half of the world's deaths due to those potentially preventable childhood illnesses occur in sub-Sahara Africa. Similarly more than one third of the deaths due to pneumonia, diarrhoeal disease and nutritional deficiencies occur in this region. It is generally recognised that weak or non-existent infrastructure to provide medicines and vaccines to combat these illnesses is a crucial underlying factor in the causation of these deaths.

Table 2 also includes information on infectious and parasitic diseases, which are responsible for significant mortality, especially in Africa. It is the development of medicines for HIV, malaria, tuberculosis, trypanosomiasis, leishmaniasis and filariasis that are covered in detail in this article.

HIV and AIDS

Although transmission is almost exclusively heterosexual, the HIV epidemic in Africa has been explosive. For example, in Botswana, currently the world's worst affected country, AIDS was unknown until the late 80's but less than fifteen years later one in three expectant women aged 15–45 years were reported to be carrying the virus[2,3]. Of the 24 million people estimated to be infected in the world, 70% live in sub-Sahara Africa[4]. Of all the deaths due to HIV/AIDS in the world, 81% were estimated to occur in this region in the year 2000 (Table 2). HIV has overtaken malaria and war as the leading cause of death. It is impossible to explain how the epidemic could have exploded to reach such staggering levels of magnitude in only a few years unless one assumed that large cohorts of young people were infected simultaneously roughly one decade before the start of the epidemic.

Only a negligible proportion of those infected has access to anti-retroviral drugs. Availability of effective drugs could have prolonged life for many and helped to reduce the risk of both heterosexual and mother to child transmission. However, perhaps the most important obstacles to the management of HIV in the African setting are inaccessibility to highly active anti-retroviral drugs and poor health infrastructures. Recent clinical

Table 2: Death by cause in WHO regions, estimate for 2000						
Cause	**Africa**	**The Americas**	**Eastern Mediterranean**	**Europe**	**Southeast Asia**	**Western Pacific**
Infectious & Parasitic Diseases (000)	**5436**	**366**	**920**	**220**	**2872**	**643**
Tuberculosis	381	57	136	74	674	342
Malaria	966	2	47	0	51	13
Trypanosomiasis	49	0	1	0	0	0
Leishmaniasis	9	0	2	0	30	0
Lymphatic Filariasis	0	0	0	0	0	0
Onchocerciasis	0	0	0	0	0	0
Childhood Illnesses	**740**	**8**	**197**	**8**	**380**	**52**
Pertussis	166	7	57	0	63	2
Measles	452	0	81	7	202	34
Tetanus	120	2	57	0	113	17
Pneumonia	**1068**	**259**	**366**	**292**	**1340**	**540**
Diarrhoeal disease	**705**	**78**	**286**	**33**	**951**	**72**
HIV / AIDS	**2392**	**72**	**54**	**21**	**371**	**32**
Nutritional deficiencies	**151**	**62**	**48**	**19**	**129**	**33**

Adapted from: World Health Report 2001, Annex table 2, Death by cause, sex, and mortality stratum in WHO regions, estimates for 2000, World Health Organization, Geneva http://www.who.int/whr/2001/main/en/annex2/htm

trials have significantly supported and improved local laboratory infrastructure and helped to increase knowledge in the use of anti-retroviral drugs. However, relatively few clinical trials have been carried out in this part of the world.

Malaria

According to the WHO[5], malaria is by far the world's most important parasitic disease. The causative agents in humans are four species of *Plasmodium – P. falciparum, P. vivax, P. malariae* and *P. ovale*. Of these, *P. falciparum* accounts for most infections and is the most lethal. Malaria is endemic in more than 101 countries inhabited by some 2.4 billion people or 40% of the world's population. World wide, the incidence is about 300–500 million cases per year, leading to over 3 million deaths, most of whom are children under the age of 5 years. Significantly, more than 90% of malaria cases occur in sub-Sahara Africa where its therapeutic management has been complicated by the emergence of drug resistance from the 70's. The economic costs, estimated to exceed US$ 2 billion, are enormous.

A review of antimalarial drug development is interesting. The first known antimalarial drug, quinine, had been used in South America for over 350 years before it was isolated and purified in 1820[6]. The second antimalarial drug, primaquine, was discovered in 1891 in Germany. It was introduced into medical practice in 1926 but was used widely only during WWII[6]. The discovery of chloroquine was announced in the US in 1943 but after WWII it became known that it had actually been synthesised much earlier (1934) by the Germans[6]. Later, the British came up with proguanil in 1946 as part of their war effort. Halofantrine in the 1960's and Mefloquine in 1978 were the result of research by the Walter Reed Army Institute of the US[6]. Malarone (a combination of atovaquone and progruanil) came into clinical use in 1994 following the collaboration of Wellcome and the Walter Reed Army Institute.

Artemisinin compounds, discovered by Chinese scientists in 1972, appear to be the first antimalarials in recent years whose development has been unrelated to efforts to protect western armies engaged in war in malaria infested parts of the world. Artemotil, a semi-synthetic derivative of artemisinin, is the newest antimalarial[7]. It was registered in Holland in mid 2000, a consequence of the collaborative effort of the WHO, the UNDP-World Bank-WHO Special

Programme for Research and Training in Tropical Disease, the Walter Reed Army Institute of the US and the Dutch company ARTECEF BV that started in 1991 as the Artemisia Project. In summary, although people living in malaria infested areas have certainly benefited, the majority of antimalarial drugs appear to have been developed mainly to protect western army personnel *and not* for the most affected populations.

Tuberculosis

Tuberculosis (Tb) is a relatively new disease to Africa where it was introduced by the coming of the Europeans several hundred years ago. In recent years, there has been a major resurgence in its prevalence due to the immunosuppressive effects of HIV. Thus the gains made in its control have been lost and as many as 60–70% of all adult patients diagnosed to have Tb are co-infected with HIV.

The story of anti-Tb drug development is different. The discovery of streptomycin in 1943 was followed quickly by that of para-aminosalicylic acid (1946), isoniazid (1952), pyrazinamide (1952), cycloserine (1952), ethionamide (1956), rifampicin (1957), and ethambutol (1962)[8]. These drugs, combined with better living standards and less overcrowding delivered a powerful blow to the prevalence of Tb in industrialised countries raising the optimism that this disease could be eradicated in the USA by 2000.

Although Tb remained common in the developing world and the spectre of multi-drug resistant forms begged for newer drugs, the pharmaceutical industry did not show any interest in investing in research for new anti-Tb compounds for more than three decades. The lack of interest may be explained by the optimism expressed above coupled by the low likelihood of making a profitable return on investment as Tb was predominantly a disease of poor countries. However, due to the HIV epidemic, increased poverty and homelessness, immigration from countries with Tb epidemics and an increased number of residents in long-term care facilities, the USA witnessed a resurgence in Tb cases of 14% by 1985[9-11]. Increasing numbers of Tb cases in the US appear to have galvanised the pharmaceutical industry and scientific community into action. Last year alone at least five new anti-Tb drugs were under development (Table 3). The United States Centres for Disease Control and Prevention has established the Tb-trials consortium with the support of the National Institutes of Health[12]. It is therefore likely that new anti-Tb products will hit the market fairly soon.

Trypanosomiasis

African trypanosomiasis or sleeping sickness is a vector-borne disease caused by two species of *Trypanosoma, T. brucei gambiense* in west and central Africa and *T. brucei rhodesiense* in east and southern Africa. According to the WHO[13], 7 to 10 million square kilometres of Africa are infested with the tsetse fly, the specific vector. Of the 60 million people living in this area who are at risk of infection, only 3 to 4 million are under surveillance with regular examinations or access to health centres that can provide screening. The number of people infected is staggering. In 1999 estimates by the WHO put this as between 300,000 and 500,000.

Melarsoprol (Arsobal®) is the only commercial drug presently available for the treatment of advanced stage sleeping sickness cases. However, treatment with this drug is associated with an increasing failure rate, currently in excess of 20%[14]. Alternative drugs (Table 4) are either associated with major drawbacks or their cost is too high[15]. None of the drugs are available in oral formulations. The continued lack of effective and safe drugs should have long become a drug development imperative for a disease that affects millions of people and which has a case fatality rate of 100% when untreated. This

Table 3: New anti-Tb drugs in development (2000)

Drug	Brand Name	Manufacturer	Status
Interferon Gamma-1b	Actimmune	InterMune	Phase 3
Amikacin liposome	Mikasone	NeXstar Pharmaceuticals	Phase 2
Prednisolone sodium	Oraped	Ascent Pediatrics	Application submitted
Phosphate Rifapentine	Priftin	Hoechst Marion Roussel	Application submitted
Tobramycin	Tobi	PathoGenesis	Phase 2

Source: http://www.phrma.org/searchcures/newmeds/

Table 4: Drawbacks to the treatment of African trypanosomiasis using currently available drugs

Drug	Year	Use	Drawbacks
Suramin	1920	Early stage rhodesiense disease	Non-oral route Severe ADRs
Pentamidine	1949	Early stage gambiense disease	Non-oral route Severe ADRs
Melarsoprol	1949	First line for late stage rhodesiense and gambiense disease	ADRs: fatal 1–5% Non-oral route Parasite resistance
Eflornithine	1990 FDA approval	Late stage gambiense	High cost Severe ADRs Non-oral route Continued production uncertain

notwithstanding, of the 1223 new drugs that entered the market between 1975–1996, only 11 were directed at tropical diseases and only one (eflornithine) at African trypanosomiasis [16-18]. At the time of writing this article, only one drug (DB-289; Imtech International) was under development at phase one level.

Leishmaniasis

Leishmaniasis has been a cause of great suffering and death for hundreds of years. Visceral leishmaniasis (VL) or *kala-azar*, is the most severe form of the disease, which if not treated has a mortality rate of almost 100%[19]. Leishmaniasis affected 395,000 Africans in 2000 causing about 9,000 deaths that year[1]. The disease is found mostly in the Sudan (prevalence 8–13% in some areas) but also in Ethiopia and some parts of Kenya. It affects mostly children and young adults, causing a severe immunosuppression. Co-infection with HIV, because of the vicious cycle of mutual re-enforcement, threatens to make an already bad situation even worse. According to WHO estimates[20], AIDS increases the risk of VL by 100-1000 times in endemic areas yet drugs that are effective, safe and accessible are not available. The only ones in use are associated with major drawbacks (Table 5). There has been no new drug developed for leishmaniasis for more than five decades.

Filariasis

Lymphatic filariasis affects about 4 million people in Africa, South Asia, Central America and the Caribbean. However, Africa, with more than 37% of all cases represents the highest density of the disease. Ninety per cent of the infections are due to *W. bancrofti*. Lymphatic filariasis results in lymphatic blockage, progressive swelling of one or more limbs, disability and disfigurement, a condition commonly referred to as elephantiasis.

Table 5: Drawbacks to the treatment of leishmaniasis using currently available drugs

Drug	Year	Drawbacks
Sodium Stibogluconate (Pentostam™) First line	In use for about 50 years	Very expensive Not readily available Requires hospital admission Parenteral administration: non-oral route Toxicity 10–15%, fatal 2–5% Resistance
Pentamidine Second line	Since 1949	Serious toxicity (including diabetes) in 60% Requires hospital administration Mortality 7–9%
Amphotericin B Third line		Requires hospital admission Toxic: rigors, fever, anaphylaxis Expensive; usually out of reach

Another filarial infection, *Onchocerca volvulus*, causes onchocerciasis, a leading cause of blindness worldwide. Out of some 120 million people worldwide who are at risk of onchocerciasis, 96% are in Africa[21]. Of those infected, over 6.5 million suffer from severe itching or dermatitis and 270,000 are blind. Although filarial infections do not directly lead to death, they cause unimaginable human suffering (disabilities, physical disfigurement, blindness) and economic loss.

For many years diethylcarbamazepine (DEC) was the only anti-filarial drug available. Perhaps not surprisingly, research leading to its discovery started only after 1500 American military personnel had been infected with filariasis during WWII[22]. The stimulus for development of ivermectin in the 1980's is not clear. However, ivermectin has provided, for the first time, a safe and effective drug capable of reducing the number of skin microfilariae in infected people and resulting in clinical improvement and decreased transmission of infection[21].

In an unprecedented charitable move, the manufacturer of ivermectin, Merck, Sharp & Dohme, established a programme in 1987 that has already donated 65 million doses of this drug. Consequently, a new global strategy for the control of onchocerciasis has now been established that aims to administer single doses annually to affected populations. Regarding the development of new anti-filarial drugs, moxidectin and tetracycline have shown potential in some animal models while combinations of ivermectin, DEC, albendazole and levamisole are being investigated in clinical trials[23].

Discussion

This brief review shows that WWII was a major stimulus for the development of antimalarial and anti-filarial drugs primarily because western army personnel were at risk. However, since the end of WWII and the demise of colonialism in Africa, there has been little or no investment into drugs that address many of Africa's priority health problems. This trend appears to have been influenced, almost entirely, by profit considerations as most Africans live in countries with health budgets that are as low as US$50 per capita.

It is evident that infectious diseases are the leading killer of young people in developing countries. The economic and social impact of three major infectious diseases (HIV, Tb and malaria) is staggering[24]. For example, they perpetuate poverty through work-loss, school dropouts, decreased financial investment, and increased social instability. According to this information, Africa's GDP would be up to US$ 100 billion greater had malaria been eliminated several years ago.

In recent times, researchers have begun to focus on the control of mother to child transmission of HIV in Africa. Several African clinical trials have made significant contributions, especially in the use of short course therapies to block transmission of HIV from mother to child[25-28]. However, with the possible exceptions of Botswana and perhaps Uganda, the findings of these studies have yet to be translated into action and positive results at public health levels.

Sustained development is essential for the attainment of national and international security. However, neither sustained development nor security is possible unless infectious diseases that disempower large numbers of the population are controlled or eliminated. Thus, security at global level can be enhanced by eliminating the gross social inequalities that undermine the most basic right of all – the right to life.

Possible Solutions

The combined morbidity, disability and mortality due to HIV, malaria, tuberculosis, trypanosomiasis, leishmaniasis and filariasis in Africa represent a festering sore on the face of today's humanity. The world today, more than at any other period in human history, has the means and the scientific knowledge to eradicate these diseases. So why has this not happened?

Perhaps the biggest problem that needs to be overcome is that of attitude. Africa's health problems are often merely seen as "belonging to Africa and having nothing to do with the rest of humanity." Such attitudes are short sighted and fallacious. In a global village, we are all interconnected and everyone is everybody's neighbour. Infectious diseases do not respect national or international borders. Recent findings that epidemics of Tb in wealthy countries are due to foreign-born populations emphasizes this point [10-12, 29, 30]. If the world's biggest infectious killers were eradicated, there would be immeasurable benefits for all humanity and enhancement of global peace and security would become a reality. Efforts to eradicate these diseases would not only be self-serving but also a social and moral imperative.

The task being proposed is not impossible. According to the WHO three of the major diseases (HIV, malaria and Tb) can each be prevented or treated for a cost of between five cents and ten US dollars. Also many low income countries have

shown that by using available tools wisely, Tb deaths can be reduced five-fold, HIV infections by 80% and malaria by 50%[25] but the costs of the tools needed are beyond the meagre budgets of most African countries.

A feasible solution would be the formation of a global, apolitical, public-private sector partnership with one *raison d'etre*: elimination of all major infectious and parasitic diseases. Establishment of a Global Health Fund would be an essential component of such enterprise. The mandate of the partnership would need to be broad but flexible enough to address drug development and operational programmes within a context of strengthening the basic local health infrastructure and research capacity to ensure sustainability. Respected and socially responsive men and women of stature could steer the scientific expertise within pharmaceutical corporations, offset the financial risk in drug development, and guarantee markets for their products.

This proposal has several precedents, all with links to the United Nations. The first is the partnership that has resulted in the development of the newest antimalarial, artemotil. The second is the WHO, the UNDP-World Bank-WHO Special Programme for Research and Training in Tropical Diseases (TDR) and the German pharmaceutical company (ASTA Medica) – that is working together to develop an oral drug to treat leishmaniasis. The third is the Medicines for Malaria Venture or MMV, a partnership between public sector agencies, the pharmaceutical industry and the WHO/TDR. Hence private/public partnerships are not only necessary, they are feasible.

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