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Government action needed to step up research and development for world's most neglected diseases

'Neglected, and most neglected diseases affect millions of people in the world's poorest countries, yet we do not have safe, affordable and field-adapted vaccines, diagnostics and drugs to tackle them.'

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It is shocking that at the start of the 21st century, when science and technology are advancing exponentially, 35,000 people worldwide still die every day from neglected diseases such as AIDS, malaria and tuberculosis (TB), and most neglected diseases such as leishmaniasis, Chagas disease and sleeping sickness (human African trypanosomiasis [HAT]). While commercial drug companies line up to produce the next lot of 'me too' drugs for western illnesses, millions of people in poor countries are left to die needlessly from preventable, treatable tropical illnesses.

The main challenges to increasing access of medicines to poor patients in developing countries are:

- Poor-quality and counterfeit drugs
- Lack of availability of essential drugs due to fluctuating production or prohibitive cost
- Need to develop field-based drug research to determine optimum utilization and remotivate research and development (R&D) programs for new drugs for the developing world [1]

Lack of research & development in most neglected diseases

This article will concentrate on the third challenge – the need for increased R&D in drugs for neglected diseases.

Neglected, and most neglected diseases affect millions of people in the world's poorest countries, yet we do not have safe, affordable and field-adapted vaccines, diagnostics and drugs to tackle them. The only alternative is for doctors to inject or prescribe medicines that were developed over 50 years ago; some of the medicines being used are so toxic that they kill one in 20 patients (e.g., melarsoprol for sleeping sickness). Although as a doctor you are trained to do no harm, sometimes you have no choice. This lack of choice stems from the fact that R&D of new drugs for neglected diseases are not lucrative enough for drug developers. This is a totally unacceptable situation. Everyone has a right to health and treatment – people should not be excluded just because they are too poor to pay, or too few to make up a large market.

Let's put this in context. In 1990, the Global Forum for Health Research estimated that a mere 10% of global investment in health R&D (US$30 billion in 1986) was being applied to 90% of the world's health problems [101]. Although the world now spends three-times as much on health research (US$106 billion in 2001), this 10:90 gap is increasing. Furthermore, of the 1393 new medicines approved between 1975 and 1999, only 1% of those developed were for tropical diseases and TB [2,102].

Most neglected diseases

Most readers will have heard of the neglected diseases AIDS, TB and malaria, but one of the frustrating things about working for diseases

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such as leishmaniasis, Chagas disease and HAT is that not many westerners have heard of them or know of anyone who suffers from them. So before continuing, let's be clear about what we are talking about.

Visceral leishmaniasis

An estimated 12 million people in 88 countries have visceral leishmaniasis (VL) also known as kala-azar, which is a deadly disease transmitted via the bite of an infected sand fly [103]. VL is the most dangerous of the three manifestations of disease caused by the *Leishmania* parasite. VL is associated with fever, weight loss, enlargement of the spleen and liver, and anemia. If left untreated, it is nearly always fatal.

There is widespread resistance to existing drugs which are also toxic, difficult to use and expensive. For example, current 'treatment' is a pentavalent antimonial that requires a painful 30-day course of injections in hospital.

Chagas disease

Chagas disease is endemic in Latin America. It is caused by the parasite *Trypanosoma cruzi*, and is transmitted to humans via the bite and defecation of triatomine insects, through blood transfusion, or through congenital transmission. The acute phase of the disease lasts for 2 months, with few characteristic symptoms, but a mortality rate of 2–8%, especially in young children.

After the acute infection, which often goes undiagnosed, the person shows strong evidence of immunity, although often remains infected. This phase can last for as long as 10–12 years without any visible symptoms. In the following chronic phase, depending on the endemic area, approximately 20–50% of patients develop the characteristic symptoms of this phase, namely irreversible cardiac, digestive or neurologic disturbances.

Left untreated, Chagas disease is often fatal, yet the two drugs currently available, nifurtimox and benznidazole, are toxic, need to be given over 30–60 days and are ineffective in the chronic phase of the disease.

Sleeping sickness

A total of 55 million people in sub-Saharan Africa are at risk of developing sleeping sickness (HAT) and at any one time, up to 300,000 people are infected. Patients suffering and dying from HAT are typically very poor and live in rural areas with no access to healthcare. HAT is caused by one of the trypanosome species of parasite and spread via the bite of the tsetse fly.

The initial lymphovascular phase of the disease (stage 1) may be asymptomatic and difficult to diagnose, and only noticed when the parasites invade the CNS (stage 2) causing disorientation, increasing sleeping disturbances and finally coma and death.

Presently, the only way to diagnose HAT is by a lumbar puncture, and there are currently two drugs used to treat stage 2 of the disease: one contains arsenic and kills one in 20 patients, and the other is an expensive anticancer drug which can only be given by an infusion four-times a day for 14 days, thus making it virtually unavailable to those with the disease in rural Africa, where access to healthcare is minimal.

Drug research for neglected diseases

Drug research for neglected diseases falls through three gaps in the R&D process. First, when basic research into novel targets and compounds, typically coming from public laboratories, is not translated into drug compounds. Second, when successful compounds in preclinical development do not progress to clinical development. Third, when new drugs or new formulations do not reach the patients.

In the last few years, the health challenge of neglected diseases has spurred global awareness. Not-for-profit organizations such as the Drugs for Neglected Diseases initiative (DNDi), and Public Private Partnerships (PPPs) such as the Medicines for Malaria Venture and TB Alliance have been established to accelerate innovation for neglected diseases. A recent report from the Wellcome Trust revealed that 63 neglected disease drug projects underway at the end of 2004 were being conducted by such PPPs [3]. The majority of these are funded by philanthropic organizations, such as the Bill and Melissa Gates Foundation, and commenced largely in the absence of significant new government incentives and generally without public intervention. Relative to the immensity of the problem, however, this response is woefully insufficient. How long can patients rely on generous philanthropy while wealthy and disease-endemic governments remain only marginally involved?

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There is an urgent need to support the new model of neglected disease drug development, which is already generating new drugs, is highly cost effective and, as the Wellcome Trust report explains, appears to offer the highest health value. Responding to the needs of the most disadvantaged populations is, at the end of the day, a public responsibility. Private, for-profit and nonprofit entities have a lot to contribute, but cannot be accountable for the lack of adequate response.

Government will & leadership

There must be very few readers who have not heard about the current 'avian flu epidemic' scare. To put things into perspective, very few people have died of the illness yet, but the whole world, including governments of rich countries and the pharmaceutical industry, have been collaborating to do something to combat it. It is amazing what can be done when an infectious disease potentially threatens the West.

One of the most interesting fallouts from this is increasing demand from governments for generic drugs, as they consider the price of the only available drug, Tamiflu® (produced by Roche at US$60 per course of treatment), unacceptable. At the time of writing, in an interesting turn of events, Roche has agreed to meet with four generic drug companies to discuss allowing them to manufacture Tamiflu, as countries stockpile it to prepare for a possible flu pandemic.

So, while the West struggles with the therapeutic needs of a possible future disease, 35,000 people are dying needlessly from existing infectious diseases every day.

Another example, the epidemic of severe acute respiratory syndrome (SARS) a few years ago, clearly showed that biomedical knowledge and the pharmaceutical sciences can be mobilized to achieve rapid advances relevant to social needs if sufficient resources and the political will can be mustered [4]. A diagnostic test for the SARS virus was developed by the international community in only 3 months.

Research & development appeal

The eight richest nations of the world have committed to providing 'as close as possible' universal access to HIV/AIDS treatment and to tackle malaria and TB and other neglected diseases. This reference to 'neglected diseases' in the G8 Communiqué is heartening. We hope that, for once, promises will be fulfilled. In the meantime, in association with Oxfam and the Biological Innovation for Open Society (BiOS) Initiative, DNDi and its Founding Partners (Médecins Sans Frontières, Indian Council of Medical Research, Kenya Medical Research Institute, Oswaldo Cruz Foundation Brazil, Malaysian Ministry of Health, Institut Pasteur and UNICEF–UNDP–World Bank–WHO Special Programme for Research and Training in Tropical Diseases) are leading an appeal calling on governments to boost innovation for neglected diseases. We are asking for their support in three specific areas.

> 'As people concerned about the wellbeing of patients in the poorer regions of the world, please lend your support to the appeal...'

Political leadership

Making global health and medicines a strategic sector and setting R&D priorities according to the needs of patients. Only then can the world achieve the Millennium Development Goals that include significant progress in combating HIV/AIDS, TB, malaria and other neglected diseases.

Sustained financial support

Governments, rich and poor, in addition to inter-governmental organizations, should provide, on a sustainable basis, the US$3 billion a year needed to reach an appropriate level of health research for diseases that affect poor people [104]. Governments should establish and design funding mechanisms to secure long-term success.

New rules to stimulate essential health research & development

Redirecting current scientific knowledge and expertise to neglected diseases will mean a substantial shift in the way essential health products are valued, financed and made available. A new enabling framework should include access to knowledge, chemical compounds and research tools that are currently protected by intellectual property rights [105]. At the heart of this should be technology transfer and research capacity strengthening in disease-endemic countries. Furthermore, governments should play a role in the streamlining of the regulatory approval processes in order to rapidly deliver essential medicines to patients. To facilitate this, the risks and benefits of each drug or vaccine must be assessed in relation to the needs of patients, the severity of the disease and the availability of treatments.

Conclusion

The current threat of an avian flu epidemic shows that governments can take a strong lead when it is in their best interests to do so. The aim of our R&D appeal is to make governments act urgently to address the critical lack of drugs for neglected diseases, which affect poor people throughout the world. We are in the process of collecting signatures to present to member states at the World Health Assembly in May 2006. As people concerned about the wellbeing of patients in the poorer regions of the world, please lend your support to the appeal by signing up at [106]. Your signature counts. Without bold new steps, disease will continue to ravage the developing world with drastic global consequences.

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