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High Time to Take Action

Research on Neglected Diseases

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Infectious and parasitic diseases affect almost exclusively poor and marginalized populations living in settings where poverty is widespread and resources or access to livelihood opportunities are scarce (1). Hence, women, children, ethnic minorities as well as people living in remote and isolated communities with no access to health care or basic services for education, nutrition, housing, clean water and sanitation are amongst those most affected. Such diseases constitute a serious obstacle to socioeconomic development and quality of life at all levels.

It is estimated that those living in absolute poverty (on less than one dollar per day) are five times more likely to die before reaching the age of five, and two and a half times more likely to die between the ages of 15 and 60. Infectious and parasitic diseases account for 25% of the disease burden in low- and middle-income countries, compared to only 3% in high-income countries. According to the World Bank, eliminating communicable diseases would almost completely level the mortality gap between the richest 20% of the world population and the poorest 80%.

A typical feature is that such diseases impair or permanently disable a large number of people, but cause comparatively few deaths. Many of these diseases have a silent chronic progression and thus do not elicit a ”health care seeking” behavior in the affected individuals. Looking for treatment is therefore frequently delayed until an advanced stage of disease, often also for fear of the social consequences. A further characteristic and a direct cause of the social distribution of those diseases is the lack of incentives to develop drugs and vaccines for markets that can not pay.

Defining neglect

International attention is currently mainly focused on the ”big three” of HIV/AIDS, malaria and tuberculosis, but attention to other infectious diseases, which have a very strong negative impact on poor populations, is neglected. Neglected diseases are neither perceived as priorities by the health systems of developing countries nor by sponsoring international agencies and philanthropic organizations and they escape especially the attention of the pharmaceutical

industry. The case is further complicated by the fact that the control of these diseases very often depends on special strategies that many times are not easily adaptable to an integrated health care system. Therefore they require special attention when the research agendas are set and development of new tools discussed.

So far, there is no generally accepted definition of neglected diseases. There are several attempts which look at the problem from different angles. A valid approach from the research point of view is to define neglected diseases as those for which there is an insufficient market or political status to drive adequate private sector and public sector research and development (R&D). Depending on the source a quite large number of diseases may fall into this category, like human African trypanosomiasis, buruli ulcer, Chagas disease, dengue fever, filariasis, guinea worm, leishmaniasis, leprosy, malaria, onchocerciasis, rabies, schistosomiasis and tuberculosis.

Not all of the diseases represent, however, the same state of emergency: Whereas the epidemiological situations for human African trypanosomiasis, dengue fever and leishmaniasis are getting worse, the global burden of leprosy, Chagas disease and onchocerciasis is declining as a result of effective control. For other diseases the epidemiological situation has greatly improved in some regions of the world but is getting worse in others (e.g. schistosomiasis and malaria).

A small number of diseases, including human African trypanosomiasis, Buruli ulcer, Chagas disease, and Leishmaniasis, are sometimes called ”most neglected” because these patients are so poor that virtually no market exists and no commercial interest will be able to stimulate research or the interest of drug companies. A common characteristic of those diseases is that they are less ”global” in their epidemiology than the ”big three” of HIV/AIDS, Tb and malaria.

The prevalence of infectious diseases can be tackled through access to functioning health care facilities, and/or the provision of clean water, sanitation systems and large scale vaccination or control programs, depending on the nature and transmission of the disease. For the majority of the diseases referred to as ”most neglected” adequate treatment is crucial, not only for the individual patient, but also as part of disease control measures.

However, the predominant problem is the lack of effective and affordable control tools: available drugs are toxic, expensive, and not very effective or losing their effectiveness because of increasing drug resistance, sometimes diagnostics have poor performance or practical limitations, and effective vaccines do not exist or if promising at all are in very early development stage. Therefore, the principal research output needed for those diseases, besides a sound understanding of their true impact, are new and improved diagnostic tools and treatments, combined with disease specific implementation strategies.
The following paragraphs elucidate the difficulties which have to be overcome in the development of new drugs and make clear the need for financial as well as political support from government levels.

The drug development perspective

In the past 25 years, 1393 new chemical entities came on the market worldwide. Thereof only 13 drugs (1%) were for tropical infectious diseases, and 3 for tuberculosis. 10 of the 13 drugs were developed for veterinary or military purposes, leaving only three that were the result of genuine efforts to create drugs for neglected diseases.

Overall, the biggest advance in drug R&D in terms of new chemical entity outputs for neglected diseases has been in malaria, for which four new chemical entities have been approved between 1975 and 1999, and a number of projects are in clinical development. Malaria represents the largest proportion of public and private research expenditures for tropical diseases (including research on drugs, vaccines, environmental interventions, and vector-control programs).

For the period considered, the number of new chemical entities per million DALYs (2) was 0.55 for infectious and parasitic diseases, compared with values between 1.25 and 1.44 for the main diseases in high income countries. The development of drugs against HIV/AIDS profited from a serious political commitment and the motivation of the pharmaceutical industry by the high potential return on investment in high-income countries. Therefore the ratio for all infectious diseases combined was mostly accounted for by the 20 antiretroviral drugs developed in the past 5 – 15 years. For tuberculosis and malaria, the numbers of new chemical entities per million DALYs are as low as 0.1, and for the most neglected diseases (e.g. sleeping sickness, Chagas disease, leishmaniasis and Buruli ulcer) the figure is virtually zero. In brief, calculated on the basis of the disease burden, there is a 15 fold difference in the number of new drugs brought to the market, even if such an important disease as malaria is taken for comparison.

An empty pipeline...

There is no indication that drug development for the most neglected diseases by pharmaceutical companies will significantly improve in the near future. A recent study by the DND (3) working group and the Harvard School of Public Health questioned the world's top 20 pharmaceutical companies on their R&D activities for malaria, tuberculosis, African trypanosomiasis, Chagas disease and leishmaniasis. 11 companies responded, representing 29% of the worldwide pharmaceutical market for 2002. Of these companies, 7 reported spending less than 1% of their R&D budget over the previous year on any of those five diseases, and eight spent nothing on the most neglected diseases (African trypanosomiasis, Chagas' disease and leishmaniasis). None of the responding companies has brought a drug to market in the last five years for any of the most neglected diseases included in the survey.

Similar results were obtained by surveys on new medicines in development conducted by the US drug industry lobby group, PhARMA (4). Of the 137 medicines for infectious diseases in the pipeline during the year 2000, only one mentioned sleeping sickness as an indication, and only one mentioned malaria. There were neither new medicines in the pipeline for tuberculosis or leishmaniasis, nor were any chemical compounds screened for usefulness against sleeping sickness, Chagas disease or leishmaniasis.

The increasing costs for drug development and the need for high financial return on investment in the pharmaceutical industry will rather aggravate this situation. Currently, the costs for development of one new drug are estimated to be in the order of US$ 800 Mio. In a commercial context this includes items like opportunity costs, projects abandoned, funds invested into research on topics relevant for the development of the company's portfolio, and all calculations are based on a full cost strategy. As a result, economic reasons for the abandonment of ongoing development programs became more prevalent over the last decade, amounting to more than 30% of the programs cancelled.

Calculating differently

The cost calculations for the development of drugs against neglected diseases include a different set of expenses: First, it is hoped that lead compounds can be secured from academic research or from abandoned industrial projects. Second, even if development programs nowadays usually follow the international quality requirements also for the development of drugs against tropical diseases they may be carried out by specialized, smaller scale organizations, part of them not-for profit. Third, the size of the total development program and thus the total patient number involved may be smaller due to the severity of the diseases and the urgent medical need, changing the balance of a risk-benefit assessment. Finally, the opportunity costs are not part of the estimates. As a result the costs for the development of one new chemical entity to a registered drug against a neglected disease were recently estimated to be around US$ 30 - 40 Mio. In comparison with commercial drug development, this is a very modest investment, however, in an area where funding is scarce it still presents a major obstacle.

The almost general absence of large scale, professional drug developing organizations hampers the development process. Drug development is divided into different stages, from the research and discovery process, through so called pre-clinical testing usually involving animals and the three phases of clinical testing in humans, to the registration process. All tasks are highly specialized and usually carried out by different entities of a company or contract research organizations. Developing a new drug from basic research is not only a capital-intensive, but also complex and time-consuming activity. In order to produce one successful drug, thousands of candidate-compounds and successive selections based on biochemical properties, safety, clinical performance, and market considerations may be needed.

Figure 1: The research Gaps (adapted from DNDi)

Figure 1 outlines this process and the gaps that occur when market prospects are low. The public research community, namely universities and institutes, is primarily involved in the processes of basic research, drug discovery and giving expert advice during the process of product development. The technical expertise, infrastructure and management capacity for

moving these discoveries through the drug development process is concentrated in the private sector. Thus, final drug development is largely conducted by private industry, according to its own priorities.

The research gaps

A closer examination of the drug development process shows exactly where the system of drug development against neglected diseases is disrupted:

1. Basic research including the carry over of discovered active compounds into pre-clinical development;
2. the carry-over of compounds from pre-clinical into clinical development; and
3. the registration of drugs to make them available to patients.

Basic research leading to discovery of active compounds has traditionally been publicly funded. However, the majority of the funding is addressing health problems in the wealthy countries. While some government money has been devoted to diseases affecting developing countries, it is a pittance compared to overall spending on drug development. Private philanthropy has in recent years sought to fill in a bit of this gap, but it is not sufficient and cannot and should not take the place of public support. Especially in the area of the most neglected diseases only a small number of research teams are active and funding is very difficult. It is also in this field where governments must get involved in restarting R&D by creating and supporting structures designed to develop essential medicines for diseases that are being sidelined by the private sector.

Pre-clinical and clinical development according to current international rules is a very specialized and costly task. It is in this field where the public-private partnerships (PPP) are most successful. PPPs attempt to foster R&D for neglected diseases by mobilizing expertise, capacity, and funding from both the public and private sectors. Typically, the PPP plays a coordinating and management role around a disease-specific R&D agenda, tries to take advantage of appropriate push and pull mechanisms, and seeks a combination of public funding, philanthropic donations and donations from industry. Major examples of this type of approach are the Medicines for Malaria Venture (MMV), the Global Alliance for TB Drug Development (GATB), and International AIDS Vaccine Initiative (IAVI), and the recently founded DNDi (Drugs against Neglected Diseases Initiative) which will focus on neglected diseases and most neglected diseases.

Outlook and perspectives

At the occasion of a major strategy and policy meeting and workshop on neglected diseases recently organized in Berlin by WHO, the Assistant Director-General for Communicable Diseases of WHO, Dr. Anarfi Asamoa-Baah, expressed his conviction that the situation is beginning to change. The threat posed by infectious diseases has become more menacing and more universal through the appearance of new and re-emerging diseases and drug resistance.

As a consequence there have been noticeable changes in how these diseases are perceived by the international community, resulting in an increased willingness to take action. Promising new collaborations, many in the form of focused PPPs, have been formed, but whereas the response to HIV/AIDS, Tb and malaria has become global and with a significant degree of coordination, the response to most of the neglected diseases still has been patchy.

Even if this approach is still fragile, there are valid examples including the drug donation programs supporting control partnerships against lymphatic filariasis, trachoma and human African trypanosomiasis. In addition, more mature programs against neglected diseases like onchocerciasis and leprosy have demonstrated that success is possible even under extremely challenging conditions.

Evidence-based, cost-effective strategies are the cornerstone of any successful disease intervention strategy. Unfortunately this basis is not available for a number of the most neglected diseases and must be developed urgently. Arguments about their economic impact may be the only way to sell them nationally and internationally and in this light the cost of doing nothing should also be quantified.

Conclusions

One major conclusion of the mentioned workshop was that international policies guiding economic and public health investments are starting to recognize the importance of neglected diseases. Still, many governments in disease endemic countries do not yet fully appreciate the significance of these diseases, whether measured in terms of human suffering or calculated as direct or indirect economic costs. A caveat hampering the promotion for understanding of the extent of the problem, and limiting support to its resolution is that existing assessment tools, such as DALYs, do not fully capture the broad impact that neglected diseases have on economics and development. Therefore, convincing evidence quantifying the size and true dimensions of the burden is urgently needed for further argumentation.

In recent years the public health debate has been largely focused on HIV/AIDS, malaria and tuberculosis. While this is understandable, it is crucial to highlight that other infectious and parasitic diseases remain amongst the primary causes of death and disability world-wide according to the 2000 World Health Report. Under this perspective it was suggested to group the most neglected diseases, despite their very much different epidemiology and approaches to control, in order to attract the necessary attention. One common entity of these diseases is that they affect the poorest segment of the world's population. Consequently it was recommended that they should form an integral part of all future pro-poor policies. A second common aspect identified is their less global distribution compared to the "big three" and their often silent and chronic progression which make them much less publicly prominent.

The great need for support to drug development against the major infectious diseases is not contested, but there is a blunt emergency in the treatment of the most neglected diseases. Only a very small number and clearly too few organizations are involved in the drug discovery

and development process for drugs against those diseases. It can therefore be expected that any financial involvement in this sector will yield a far above average return on investment in terms of midterm improvement of the patient situation.

It is obvious that the multinational pharmaceutical industry cannot be solely relied on to develop the medicines required to treat the diseases that affect the world's poor. The establishment of PPPs and new organizations to address R&D of drugs against neglected diseases, e.g. the Drugs for Neglected Diseases initiative DNDi or the Institute for One World Health, offer a good approach in the right direction. Also, some significant initiatives supported by the Gates Foundation to promote drug development or to strengthen research and control like the UNC (5) lead Consortium to Discover new Drugs for the Treatment of Parasitic Diseases (with a strong involvement of the Swiss Tropical Institute), the Malaria initiative at the London School of Hygiene and Tropical Medicine or the schistosomiasis control initiative at the Imperial College London offer very promising approaches.

However, funding and policy making should not become solely the responsibility of private organizations and foundations. The World Health Organization continues to be active in the field through its Special Programme for Research and Training in Tropical Diseases (TDR), but also governments must ultimately become involved for ensuring that people's health needs are met. Governments can make a difference as they have the power to influence drug development, through both, direct research funding and policies to influence the activities of the private sector. This is why they must also take action when the private sector or the market fails.

In conclusion, a major task will now be to awake the international organizations and the interest of donor agencies which have often shied away from investing in drug development against the most neglected diseases because they did not perceive it as a part of their mandate, because of the complicated consortium structures involving public and private partners, and because of the resulting programs in backward areas on account of poor governance, weak health infrastructure and consequently higher risk of failure.

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Notes:

1. World Health Report 2000, Health Systems: Improving Performance
2. DALYs - Disability Adjusted Life Years (the number of healthy years of life lost due to premature death and disability)

3. DND - Drugs for Neglected Diseases
4. PhARMA - The Pharmaceutical Research and Manufacturers of America
5. University of North Carolina, Chapel Hill

The Pharmaceutical Medicine Unit of the Swiss Tropical Institute

Recognizing the urgent need for new and better vaccines and drugs to prevent and treat infectious diseases in developing countries a number of initiatives have been launched. Furthermore global pharmaceutical companies are entering donation programs and agreements with international organizations to provide the poorest countries with drugs against infectious diseases (e.g. Aventis and WHO). Those activities have created an increasing demand for the conduct of clinical trials in developing countries.

The design and conduct of clinical trials in Northern countries like Europe, the United States and Japan follows largely harmonized guidances. The conduct of clinical trials in developing countries requires, in addition to a profound knowledge of those international regulations, a specialized expertise to address the technical, ethical, cultural and logistical difficulties and constraints.
The Pharmaceutical Medicine Unit of the Swiss Tropical Institute offers selected services in the design, organization, conduct and/or monitoring of clinical trials with a main focus on trials concerning tropical diseases in developing or industrialized countries.

www.sti.ch/scih/pharmaunit.htm

International Programmes dealing with Neglected Diseases:

www.dndi.org - "The DNDi will develop new drugs or new formulations of existing drugs for patients suffering from the most neglected communicable diseases. Acting in the public interest, it will bridge the existing R&D gaps in essential drugs for these diseases by initiating and coordinating drug R&D projects in collaboration with the international research community, the public sector, the pharmaceutical industry, and other relevant partners."

www.who.int/tdr - "The Special Programme for Research and Training in Tropical Diseases (TDR) is an independent global programme of scientific collaboration. Established in 1975 and co-sponsored by the United Nations Development Programme (UNDP), the World Bank and the World Health Organization (WHO), it aims to help coordinate, support and influence global efforts to combat a portfolio of major diseases of the poor and disadvantaged."

www.oneworldhealth.org - “We challenge the assumption that pharmaceutical research and development is too expensive to create the new medicines that the developing world desperately needs. By partnering and collaborating with industry and researchers, by securing donated intellectual property, and by utilizing the scientific and manufacturing capacity of the developing world, OneWorld Health can deliver affordable, effective and appropriate new medicines where they are needed most.”

www.tballiance.org - “The Global Alliance for TB Drug Development is a public-private partnership driven to halt the rise and reverse the spread of the world’s oldest infectious disease by developing new, faster-acting and affordable tuberculosis medicines.”

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