Drug development for neglected diseases: a deficient market and a public-health policy failure

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There is a lack of effective, safe, and affordable pharmaceuticals to control infectious diseases that cause high mortality and morbidity among poor people in the developing world. We analysed outcomes of pharmaceutical research and development over the past 25 years, and reviewed current public and private initiatives aimed at correcting the imbalance in research and development that leaves diseases that occur predominantly in the developing world largely unaddressed. We compiled data by searches of Medline and databases of the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products, and reviewed current public and private initiatives through an analysis of recently published studies. We found that, of 1393 new chemical entities marketed between 1975 and 1999, only 16 were for tropical diseases and tuberculosis. There is a 13-fold greater chance of a drug being brought to market for central-nervous-system disorders or cancer than for a neglected disease. The pharmaceutical industry argues that research and development is too costly and risky to invest in low-return neglected diseases, and public and private initiatives have tried to overcome this market limitation through incentive packages and public-private partnerships. The lack of drug research and development for “non-profitable” infectious diseases will require new strategies. No sustainable solution will result for diseases that predominantly affect poor people in the South without the establishment of an international pharmaceutical policy for all neglected diseases. Private-sector research obligations should be explored, and a public-sector not-for-profit research and development capacity promoted.

Despite progress made in both the basic knowledge of many infectious diseases and the process of drug discovery and development, tropical infectious diseases such as malaria, leishmaniasis, lymphatic filariasis, Chagas’ disease, and schistosomiasis continue to cause significant morbidity and mortality, mainly in the developing world. The burden of infectious diseases has been compounded by the re-emergence of diseases such as tuberculosis, dengue, and African trypanosomiasis. These diseases all predominantly affect poor populations in the less-developed world.

WHO has identified three key factors that can collectively contribute to the burden of illness associated with infectious diseases: failure to use existing tools effectively, inadequate or non-existent tools, and insufficient knowledge of the disease. The discovery and development of most of the current tropical pharmacopoeia was driven by colonial requirements during the first part of the 20th century. As Western interests drifted away from these regions, tropical diseases have become progressively neglected, mainly because they do not offer sufficient financial returns for the pharmaceutical industry to engage in research and development. Tuberculosis—another major poverty-related disease—is also neglected in terms of drug research and development.

Despite an ever-increasing need for safe, effective, and affordable medicines for the treatment of these diseases, drug development has virtually stopped.1,2 We present an analysis of the trends in drug development over the past 25 years, focusing particularly on neglected diseases, and review future prospects for stimulating research and development through analysis of current public and private sector initiatives aimed at correcting this imbalance in research and development.

Drug development over the past 25 years

We did a quantitative and qualitative analysis of global drug development output over the past 25 years, focusing specifically on neglected diseases. Data on the new chemical entities marketed in this period were compiled by searches of Medline and databases of the US Food and Drug Administration and the European Agency for the Evaluation of Medicinal Products. The data are presented over time and by therapeutic class, indicating innovation level and market share in both absolute terms and relative to the burden of disease expressed as millions of disability-adjusted life-years (DALYs). Although rare, examples of registrations exclusively within developing countries do exist—eg, artemisinin derivatives for malaria developed and manufactured in China.

We found that 1393 new chemical entities were granted a market authorisation between 1975 and 1999 (table I). Their quantitative distribution in different therapeutic areas shows a bias towards high-income countries. This imbalance was especially pronounced for infectious and parasitic diseases, which account for a third of the worldwide disease burden but only 5% of the disease burden in high-income countries. To quantify the level of...
Full text of the document is not available in the provided image.
ment for all neglected diseases, six research and development projects can be classified as mid-late development projects, and an additional 12 early development projects are ongoing. This number compares with an estimated 2100 compounds in clinical development for all other diseases during 1999–2000.3

There is no indication that drug development for neglected diseases will significantly improve in the near future. A recent study by the Drugs for Neglected Diseases working group (an independent group established by Médecins Sans Frontières to examine drug development for neglected disease) and the Harvard School of Public Health questioned the world’s top 20 pharmaceutical companies on their research and development 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, seven reported spending less than 1% of their research and development budget over the previous fiscal year on any of the five diseases, and eight spent nothing on the three most neglected diseases (African trypanosomiasis, Chagas’ disease, and leishmaniasis).4

Overall, the biggest advance in drug research and development and 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 18 projects were in clinical development in 2001. The new approaches to antimalarial therapies rely mainly on artemisinin derivatives discovered in China in the 1990s, which are particularly effective in combination with other drugs in slowing the development and spread of drug resistance. Malaria represents the largest proportion of public and private research expenditures for tropical diseases (includes research on drugs, vaccines, environmental interventions, and vector-control programmes) and accounted for 56% of the 1988–99 Tropical Disease Research (TDR) budget, 2% of the total US National Institutes of Health budget, and 4% of the UK Wellcome Trust’s budget.7 The other neglected diseases are poor relatives when compared with malaria (table 3).

Moreover, the mean time for clinical development is longer for neglected diseases than for other indications. In the USA, the mean time for clinical development during the 1990s was 8·8 years for neglected diseases, compared with 5·4 years for other indications.13 The comparatively poor performance is attributable to the low market viability of these compounds, and hence suboptimum funding compared with potentially more profitable projects. Whereas the development of all 16 new chemical entities for neglected diseases received at least some level of public-sector support, this sector is also failing: thus far there is no example of the public sector as applicant for a drug registered for a neglected indication (although a submission to the US, UK, and Swiss authorities made in 2001 by TDR for rectal formulation of artesunate is awaiting assessment).

The data presented here quantify the degree of neglect and poor outcome in terms of drugs to control the infectious diseases that disproportionately affect impoverished populations. Although substantial advances in molecular biology and pathophysiology have been made—including the ongoing genome sequencing of the parasites that cause malaria, leishmaniasis, and African trypanosomiasis—these advances are not translating into new products directed at the needs of patients.11,12 More is known and published on the biology of leishmania and trypanosomes than any other parasite, yet virtually no products result from this wealth of knowledge.13 This absence is mainly a consequence of inadequate investment in drug research and development for neglected diseases.

**Table 3: Drugs under clinical development for a neglected-disease indication in 2001.**

<table>
<thead>
<tr>
<th>Disease</th>
<th>Early development *</th>
<th>Mid–late development</th>
<th>Studies with registered entities</th>
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</thead>
<tbody>
<tr>
<td>Malaria</td>
<td>Chlorproguanil/dapsone/artsunate (Liverpool University [UK], GSK, TDR, MMV)</td>
<td>Chlorproguanil/dapsone (TDR, GSK, DFID, WHO)</td>
<td>Artesunate/mefloquine (WT, TDR, MSF)</td>
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<td></td>
<td>Pyronaridine/artsunate (TDR, Shin Poong, MMV)</td>
<td>Pyronaridine (Tulane University [TX, USA])</td>
<td>Artesunate rectal (TDR, Knoll Shering, Scangarm, Novartis)</td>
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<td></td>
<td>Modified side-chain chloroquine (Tulane University [TX, USA])</td>
<td>Dihydroartemisinin (Arteceft BV)</td>
<td>Artesunate/sulfadoxine/prymethamine (TDR, MSF, IDA, WT)</td>
</tr>
<tr>
<td></td>
<td>Dihydroartemisinin (Arteceft BV)</td>
<td>..</td>
<td>Artesunate/amodiaquine (TDR, MSF)</td>
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<tr>
<td></td>
<td>Fosmidomycin (Jomaa Pharmaka GmbH, TDR)</td>
<td>Dihydroartemisinin/piperazine (Guangzhou University [China], WT, WHO)</td>
<td>Dihydroartemisinin/mefloquine (Thai Government, TDR)</td>
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<tr>
<td></td>
<td>Desbutyl halofantrine (GSK)</td>
<td>..</td>
<td>Artesunate/atavaquone/proguanil (WT)</td>
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<td></td>
<td>..</td>
<td>..</td>
<td>Azithromycin combinations (WRAIR, NIH, Pfizer)</td>
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<tr>
<td>Leishmaniasis</td>
<td>Siltamazole (WR6026: WRAIR, GSK)</td>
<td>Paromomycin (TDR, IOWH, MSF, IDA)</td>
<td>Amphotericin B liposomal (Cornell &amp; Banaras Hindu University [India])</td>
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<tr>
<td>(visceral)</td>
<td>..</td>
<td>Miltefosine oral (TDR, AstaMedica)</td>
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<tr>
<td>Onchocerciasis</td>
<td>Moxidectin (TDR)</td>
<td>..</td>
<td>Ivermectin/albendazole (TDR)</td>
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<tr>
<td></td>
<td>Oral eflornithine (Aventis, TDR)</td>
<td>..</td>
<td>Ivermectin/levamisole (TDR)</td>
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<td></td>
<td>..</td>
<td>..</td>
<td>Albenzaole/levamisole (TDR)</td>
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<td></td>
<td>..</td>
<td>..</td>
<td>Ivermectin/doxycycline (TDR, Nocht Institute [Germany])</td>
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<tr>
<td>Lymphatic</td>
<td>..</td>
<td>..</td>
<td>Ivermectin/albendazole (TDR)</td>
</tr>
<tr>
<td>Filariasis</td>
<td>..</td>
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<td>Ivermectin/doxycycline (TDR, Nocht Institute)</td>
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<tr>
<td>Schistosomiasis</td>
<td>Arteether (TDR)</td>
<td>..</td>
<td>Albenzaole/diethylcarbamazine (TDR)</td>
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<tr>
<td>Chagas’ disease</td>
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<tr>
<td>Tuberculosis</td>
<td>Oxofloxacin/rifampicin (TDR)</td>
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Sources: WHO; Special Programme for Research and Training in Tropical Diseases (TDR); GSK=GlaxoSmithKline; MMV=Medicines for Malaria Venture, Switzerland; WT=Wellcome Trust, UK; MSF=Médecins Sans Frontières; WRAIR=Walter Reed Army Institute of Research, USA; IDA=International Dispensary Association, Netherlands; IOWH=International One World Health; DFID=Department for International Development, UK; NIH=National Institutes of Health, USA. *No absolute distinction can be made between early and mid–late development.
diseases. For example, investment in research for malaria, at $42 per fatal case, is at least 80 times lower than for HIV/AIDS and 20 times lower than for asthma.14 The other neglected diseases lag even further behind.

Current incentives and technology transfer

The pharmaceutical industry argues that research and development is a “costly and risky activity.”13 This argument is put forward to explain the lack of research and development into diseases of the poor, and to justify the high price of new chemical entities. Developed countries offer viable market incentives for research and development through individual purchasing power and purchasing through government-run health insurance programmes. In Europe, for instance, these mechanisms cover two-thirds of drug costs for 80–100% of the population14 as opposed to 35% in Latin America and less than 8% in Africa.15 With public spending on drugs at around $239 per head per annum in countries belonging to the Organisation for Economic Cooperation and Development (OECD), the pharmaceutical industry has a strong incentive to develop drugs for this market. By contrast, most developing countries spend less than $20 per year and per head on all health-care expenditure, less than $6 in sub-Saharan Africa, including drug expenditures16). This situation results from a market too small to attract private-sector investment in research and development for the diseases that mainly affect developing countries.

Measures envisaged to overcome this limitation in both public and private markets are either incentives devised to encourage private investment towards the development of new cost-effective drugs (often referred to as push and pull mechanisms), or public-private partnerships.

Push mechanisms are incentives that operate upstream during the research and development process, and involve costs to the public sector without a guarantee that a viable drug will be delivered (such as tax credits for and public investment in research and development, which lower the cost). Pull mechanisms operate downstream, and offer public incentives for development of a product (examples include patent extensions and advance purchase commitments). In exchange for this increased market attractiveness or market subsidy, private pharmaceutical companies are expected to increase their research and development efforts.10 There are examples of push and pull mechanisms, or a blend of the two, being applied to areas of the pharmaceutical sector with variable effects.

Orphan drug legislation is an example of push and pull elements combined, which uses a blend of tax credits, market exclusivity, and intellectual property protection. The US Orphan Drug Act, which grants market exclusivity for rare diseases of national public-health priority in the USA, is generally regarded as a domestic success story.12 Drawing a parallel between rare and neglected diseases drugs is tempting. However, orphan legislation operates within a market logic: reasons for success in the USA, are inapplicable in the countries mainly affected by neglected diseases, and so far no drug candidates for a neglected disease indication have been developed and marketed through US and European orphan legislations.17 Moreover, market prices for orphan drugs are extremely high (the annual cost of life-long treatment with alglucerase for Gaucher’s disease is about $150 000 per patient13), whereas the average annual per-head health-care expenditure in sub-Saharan Africa is currently $6.14 Push mechanisms might contribute to fast-track research and development or give a wealth of new lead compounds through public investment. But if there is no viable market for these candidate drugs (patient or government purchasing power), there will be no incentive to develop them further. In the USA, 39% of new chemical entities in clinical development are abandoned because profit prospects are poor.18

Orphan-type legislation is therefore unlikely to provide the solution to drug development for tropical diseases. In any case, whether the pharmaceutical industry—one of the most profitable industrial sectors today—thanks to extended market monopolies—should be given further market incentives is to be questioned. The ongoing debate surrounding industry’s claim that drug research and development is extremely costly,21 and the uncovering of the pharmaceutical industry’s innovation deficit,22 lend further weight to such concerns.

Another mechanism that has been mainly applied to vaccines is differential pricing between industrialised and developing countries, allowing research and development investments to be recouped in wealthier countries so that lower prices can be charged in developing countries (eg, pricing at production costs plus a small margin).23 Whether differential pricing can be applied to drugs is currently being explored, but it would be unlikely to offer much for the most neglected diseases that exist exclusively in poor countries.

In 1998, more than 90% of the worldwide pharmaceutical production by value, and 97% of research and development activities, occurred in developed countries.24 With few exceptions, the countries concerned with neglected diseases lack adequate capacity to undertake research and development activities for neglected diseases. To counter this polarity, building of local research and development and production capacity through technology transfer is being examined as a tool to generate long-term solutions as well as economical development. The transfer of capacities requires an enabling environment at both the provider and the receiver end—in most cases, the private sectors of developed and developing countries. Capacity building and technology transfer has been promoted for many years by such groups as the United Nations Development Programme,25 TDR, and the Drugs for Neglected Diseases Working Group. It can be promoted via bilateral and multilateral development cooperation, but priority-setting must be well adapted to the specific needs and capabilities of the concerned countries, who themselves must place neglected diseases higher up the political agenda. Emerging economies could be the first target of action, and solutions for the poorest countries could be grafted on to successful drug production facilities in those countries.

This issue of technology transfer inevitably leads to the consequences of the implementation of provisions of the World Trade Organisation TRIPS (Trade-Related Intellectual Property Rights) agreement. Whether intellectual property rights can significantly affect technology transfer (which is included as an objective in Article 7 of the TRIPS agreement) and foreign direct investment towards developing countries is unclear.14

A broader question with respect to intellectual property rights protection is how viable it is as a system for stimulating research and development and delivering the most needed medicines. The costs to national governments of extended intellectual property protection and subsidies need to be considered. Intellectual property regimes are in essence a pull mechanism intended to promote research and development. There is no conclusive evidence that further strengthening of intellectual property rights (through for example roaming patent extensions—a proposal favoured by the
pharmaceutical industry) results in benefits to public health. In the OECD countries, between the 1980s and 1990s, the effective patent life of drugs was extended by 6 years as a result of several "patent term restoration" measures that conferred a total average patent life of 14 years from marketing (such as the Hatch-Waxman Act of 1984 in the USA and the Supplementary Protection Certificate of 1993 in Europe). But while the total number of products registered increased slightly in the same period, the mean innovation index remained unchanged (table 2). Judging from the lack of research and development for tropical diseases in the past 25 years, market incentives provided by intellectual property rights do not work when market prospects are poor or non-existent.

Regulations are an important element in the research and development process, and have been adapted by Western regulatory authorities to respond better to specific priority health needs. For example, fast-track registration was successful in speeding up the delivery of medicines for HIV/AIDS. Such measures result, in particular, in shorter review times for drugs considered as responding to health priorities: the mean approval time in the USA is 11.8 months (ranging from 26.4 months for respiratory agents to 4.6 months for AIDS antiretrovirals).

In the West, drug regulation follows strict guidelines defined by the International Conference on Harmonisation of regulatory requirements for registration of pharmaceuticals (ICH). But neglected diseases are not a priority in the West, and region and context-specific expertise and regulatory capacity is therefore needed in countries where these diseases are endemic so that review and registration of novel compounds or new chemical entities can occur in a way that is relevant to the priorities of disease-endemic countries.

For example, malaria control has improved significantly in some Asiatic countries because of the availability of new and effective drugs, notably artemisinin derivatives, registered in several disease-endemic countries. Yet corresponding drug dossiers may not strictly conform to ICH guidelines. Initiatives to harmonise drug regulation at a regional level currently underway in southeast Asia (ASEAN technical cooperation in pharmaceuticals) and South America (Mercosur treaty) are examples of initiatives that should be strengthened.

Double standards of drug quality, safety, and efficacy are not acceptable, and standards set by WHO must be adhered to as the minimum normative criteria. But guidance on regulatory procedures based more on technological advances than on nationally determined health priorities are increasingly being applied, with the net effect of inhibiting drug development capacity in the developing world. Specific procedures should be designed to allow for a better assessment of the risk-benefit ratio of drugs for neglected diseases, allowing for speedier and more effective drug development.

**Public-private partnerships**

Public-private partnerships (PPPs) attempt to fill gaps in the health needs of developing countries through the establishment of public-private collaboration, networks, and partnerships. The private sector includes for-profit (pharmaceutical companies) and not-for-profit (charities, foundations, and philanthropic institutions) groups, whereas the public sector includes international organisations, development and aid agencies, governments, and academia.

Recently, PPPs have altered the international health landscape, particularly in the pharmaceuticals sector, as a new paradigm for drug development activities. They have resulted from a gradual convergence of the private-for-profit and public sectors (under pressure of international organisations such as the World Bank), concerns engaged by the not-for-profit sector, and the pharmaceutical industry’s need to improve its image.

Traditional examples of public institutions working in partnerships include the establishment of the “Global Fund for HIV/AIDS” (1995), the “Global Fund for TB” (2001), and the “Global Fund for Malaria” (2000). Donor agencies engaged thus must not only contribute assets or funds to develop specific products.

There were various examples of ad-hoc agreements during the 1990s to develop drugs between TDR and WRAIR and drug companies, sometimes with government-donor support. However, the progressive withdrawal of the pharmaceutical industry from the tropical-disease sector widens the gaps in the drug development process, especially at the point of transition between discovery and early development. To address this problem, recent agreements between the public and private sector also focus on the discovery process, for example to access industry’s chemical libraries (such as the agreement between the Japanese pharmaceutical industry association, the Japanese government, and TDR). Most of these types of partnerships have depended on a coincidence of priorities among partners who each contribute assets or funds to develop specific products.

The most recent trend favours disease-based initiatives, as exemplified by the Medicines for Malaria Venture (which accounts for most of today’s antimalarial drug development projects) and the Global Alliance for Tuberculosis. Both initiatives focus mainly on converting drug candidates into registered entities using a social venture capital model funded by the public and philanthropic sectors. They are managed as not-for-profit ventures, operate in collaboration with several partners ranging from the traditional pharmaceutical industry to corporations, academia, and development agencies, and rely on business drug development models and a medium-term secured budget including newer sources of funding (such as the Gates Foundation).

Industry has played a part in the establishment of these new ventures, is represented through their boards, and is a development partner, contributing both facilities and assets and receiving funds. However, company engagement is limited: of the 14 active or planned projects of the Medicines for Malaria Venture, five still have no industrial partner, and six companies are involved in the remaining nine projects (GlaxoSmithKline alone accounts for three).

Much hope is placed in public-private partnerships, but it is too early to say how successful these initiatives will be. Moreover, developing a drug is one thing, but consideration must also be given to ensuring equitable access. Engagement with an industry whose strategy has so far largely been to maximise profit in the West, rather than establish an equitable pricing policy worldwide, requires careful management of intellectual property. Donor agencies, for their part, must do more to assist in drug procurement: current financial pledges to the Global Fund for AIDS, TB and Malaria, at least that one fifth of the estimated requirement, indicate that much greater political will is required.
PPP’s clearly do not provide the solution for all tropical diseases. They exist for tuberculosis and malaria because these diseases rank higher in the public-health priorities of developed countries than other, more neglected diseases and represent a potential market for industry. For other neglected diseases that do not represent a health threat to the developed world, public and private sector engagement for neglected diseases is likely to be more difficult to motivate.

Conclusions

Despite impressive advances in science, technology, and medicine, society has failed to allocate sufficient resources to fight the diseases that particularly affect the poor. There is a dearth of research and development into neglected diseases to control the re-emergence of human African trypanosomiasis, to replace the ineffective and toxic drugs for Chagas’ disease, to overcome resistance to antileishmanial and antimalarial drugs, and to develop more effective drugs for tuberculosis to shorten treatment and address multidrug-resistant disease.

Market prospects and return on investment dictate the pharmaceutical industry’s investments, leaving many medical needs unmet. Only 16 new chemical entities marketed in the past 25 years were for tropical diseases and tuberculosis, and all were developed with public-sector involvement. Whereas on average two in three new drugs developed in this period offer little or no therapeutic advance over existing treatments, all new drugs for neglected diseases represent a clear therapeutic benefit, and all are included in the WHO Essential Drug List, which indicates the importance of new drugs for neglected diseases.

National governments and international organisations have recently increased efforts to correct the imbalance between a decreasing supply and a growing demand for drugs that meet the needs of poor countries. A range of market push and pull measures are being proposed to attract the pharmaceutical industry to invest or reinvest in the neglected diseases area. In parallel, various PPPs have been established, combining respective capacities and resources. Although all such efforts are certainly necessary, their possible effect is likely to be insufficient to meet the vast and increasing health needs of poor people in the developing world.

Patent life has increased in the past 20 years, but the rate of innovation has not. Moreover, only one in three new drugs developed in the past 25 years represent a clear therapeutic advance. This finding raises the question of whether continuously increasing patent protection is an effective stimulus for innovation. The existing global patent system will clearly not answer global population health needs, and certainly will not provide the answer for neglected diseases: a market monopoly incentive is irrelevant when market prospects are absent.

The chronic neglected disease crisis calls for a substantial and long-term response, and will probably require a paradigm shift in health and research and development policy. Governments in the North and South must lead in restarting research and development for diseases that are currently ignored. A well defined, needs-driven research and development agenda is needed to assist policy makers, funding agencies, and the research community in setting priorities. These can be implemented through competent and durable research and development networks in the South, to be built or strengthened via focused capacity and technology sharing.

The private sector must also do more. There is currently an imbalance between private-sector rights and obligations under international agreements. The public sector — ie, the main buyer of pharmaceuticals — provides the private sector with patent incentives for innovation, but has little say over the research agenda. Governments can and do oblige industry to do necessary research in other sectors. A neglected-disease research obligation could be framed that would require industry to reinvest a percentage of pharmaceutical sales into neglected disease research and development, either directly or through public programmes.

For the most neglected diseases such as African trypanosomiasis or leishmaniasis, which might not account for much of the global disease burden, but which represent a significant disease burden in affected countries, a new approach is needed. The Drugs for Neglected Diseases working group is currently exploring the feasibility of an international not-for-profit initiative that would focus on drug development projects for the most neglected diseases. Such an initiative would remove the process of researching and developing life-saving drugs from a market-driven logic. Without a shift to needs-driven research and development, the needs of millions in the developing world will continue to be ignored.

Conflict of interest statement

None declared.

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References

Uses of error

The tip of the iceberg?

J Eikelboom

I was a medical student on my first clinical rotation and the patient was a confused elderly male who needed a urinary catheter. The houseman gratefully accepted my offer of assistance and disappeared to attend to other duties. I should have realised that something was amiss when the patient groaned during inflation of the balloon. However, I reasoned that a 16 French catheter couldn’t possibly be comfortable, and ignored the signs. Several hours later, the consultant noticed blood seeping around the catheter, and ordered deflation of the intraurethral balloon.

I was a medical intern in orthopaedic surgery, and one of my charges was an elderly male who had undergone surgery for a fractured neck of femur. For three successive nights an increasingly irate senior houseman was asked to review him for recurrent breathlessness. However, by the next morning, his symptoms had invariably resolved and the ward round barely slowed long enough to confirm that his wound was healing satisfactorily. I am still grateful that my patient survived his sojourn on the orthopaedic ward long enough to be transferred to a medical rehabilitation unit where his left ventricular failure was finally treated. While inexperience contributed to these errors, fatigue played a role in the next. I was awoken by a telephone call at 4 am to hear that the respiratory failure of a woman in her forties with pulmonary graft-versus-host-disease was getting worse. I ordered a chest radiograph and an increase in the oxygen flow rate before going back to sleep. The radiograph was not reviewed until several hours later, by which time the pneumomediastinum had caused irremediable deterioration. I am uncertain whether earlier intervention would have postponed her demise, as she died subsequently from respiratory failure. The need for adequate supervision, a more effective referral system, and improvements in working hours is self-evident.

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