FEATURE

Access to Medicines in Resource-limited Settings: The End of a Golden Decade?

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ABSTRACT

Strong international mobilization and political will drove a golden decade for global health. Key initiatives over the last decade include setting of health-related Millennium Development Goals; the Commission on Macroeconomics and Health; the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria; the Doha Declaration on the TRIPS Agreement and Public Health affirming countries' rights to protect public health when implementing patent rules; and the creation of product development partnerships to address neglected areas of research and development. Significant progress was made in reducing the incidence of and morbidity and mortality from human immunodeficiency virus (HIV), tuberculosis (TB), and malaria, with a major impact made through increased access to medicines. Antiretroviral treatment for HIV was expanded to 6.6 million people, and medication prices were reduced significantly through generic competition. However, donor support has started to decline at a time when many patients still wait for treatment and the prices of needed newer medicines are on the increase due to patent protection. TB incidence has started to decrease, but progress in diagnosis and treatment of multidrug-resistant TB has been slow due to complexity of treatment and high drug costs. Promising new TB drugs in development need to be introduced rapidly and appropriately while treatment is being expanded. The introduction of more affordable artemisinin combination therapies for malaria contributed to significantly reducing malaria incidence and mortality, but challenges remain in ensuring that the latest recommendations for treating severe malaria are implemented. Looking to the next decade, there is a worrisome mismatch between additional health priorities accompanied by shifting burdens of disease that need to be addressed and dwindling political attention and financial support. Difficulties in producing and guaranteeing access to affordable medicines are expected from a changing pharmaceutical market where an appropriate balance between trade and health has not been found. Systematic changes through a global framework for research and development and access are needed to support increased innovation and access to the health tools of the next decade.

摘要

大的国际动员和政治引导，将催生出全球健康事业的一个黄金十年。在过去的十年中，主要的初步行动包括设立联合国千年发展目标；建立宏观经济学和卫生委员会；创建抗击艾滋病、肺结核与疟疾全球基金；TRIPS协定多哈宣言，确认在保护专利实施细则时，保护公共健康的国家权力；以及建立产品开发合作关系，促进被忽视的研发领域的发展。通过提高药物供应水平，在降低HIV、肺结核和疟疾的发病率和死亡率方面取得了显著进展。HIV抗逆转录病毒疗法已经覆盖了660万人，并且通过非专利药品竞争，使得医疗价格显著降低。然而，随着更多的患者需要治疗，且患者所需的新药价格由于专利保护而上涨，捐赠者支持力度开始下降。肺结核的发病率已经开始下降，然而多药抗药性肺结核的诊断和治疗进展缓慢，其原因是治疗的复杂性和较高的药物花费。当前，随着治疗范围的扩大，需要在恰当时机迅速引入的新药物正在研发之中。青蒿素组合治疗是一种更廉价的疗法，该疗法的引入显著降低了疟疾的发病率和死亡率，但是在保证实施最新的治疗严重性疟疾的卫生计划方针方面，仍面临挑战。展望下一个十年，我们看到一个令人担忧的情况，那就是伴随着疾病负担转移的附加卫生工作重点，与政策注意力和资金支持减弱之间的矛盾。随着药物市场的变化，可以预见到在生产和保证廉价药物供应方面的困难，当前的市场贸易和卫生状况之间尚未建立起恰当的平衡。全球框架内药物研发和供应的系统变化，需要支持增加创新的要求，并为下一个十年提供健康工具。

RESUMEN

Una sólida movilización internacional y política generará una década dorada para la salud mundial. Las iniciativas fundamentales de la última década incluyen la propuesta de Objetivos de Desarrollo del Milenio relacionados con la salud; la Comisión sobre Macroeconomía y Salud; la creación de un Fondo mundial de lucha contra el SIDA, la tuberculosis y la malaria; la Declaración de Doha relativa al acuerdo sobre los ADPIC y la salud pública, en el que se reconocen los derechos de los países de proteger la salud pública cuando se implementen las leyes de patentes; y la creación de asociaciones para el desarrollo de productos con el fin de tratar las áreas descuidadas de investigación y desarrollo. Se logró un progreso importante en la reducción del índice de mortalidad causada por el VIH y su incidencia, la tuberculosis (TB) y la malaria, debido al aumento de las posibilidades de acceso a los medicamentos para tratar estas enfermedades. El tratamiento antirretroviral para el VIH fue tornó más accesible y benefició a 6,6 millones de personas. Además, los precios de los medicamentos se redujeron en forma significativa a raíz de la competencia con los genéricos. Sin embargo, el apoyo de los donantes comenzó a disminuir en el momento en que los pacientes más

necesitan el tratamiento y los precios de los nuevos medicamentos están en aumento a causa de la protección de patentes. La incidencia de la TB comenzó a disminuir, aunque el progreso en el diagnóstico y el tratamiento de pacientes con cepas de TB resistentes a una variedad de fármacos ha sido lento debido a la complejidad del mismo y al alto costo de los fármacos. Se están desarrollando nuevos fármacos con efectos prometedores que deben ser introducidos con rapidez, pero de manera adecuada, mientras se amplía el tratamiento. La introducción de terapias combinadas a base de artemisinina más asequibles para tratar la malaria contribuyó en la reducción significativa de la incidencia y tasa de mortalidad de esta enfermedad; no obstante, el desafío sigue siendo garantizar que se implementen las últimas recomendaciones para el tratamiento de la malaria grave. Para la próxima década, se prevé un desajuste preocupante entre las prioridades adicionales en materia de salud, así como un costo variable de la enfermedad que se debe tratar y la atención política y apoyo económico cada vez más escasos. Se prevén dificultades para producir y garantizar el acceso a medicamentos asequibles en un mercado farmacéutico cambiante, en el que se no se ha podido encontrar un equilibrio adecuado entre el comercio y la salud. Es necesario hacer cambios sistemáticos a partir de un marco global para la investigación, el desarrollo y el acceso a los medicamentos para sustentar la cantidad de innovaciones cada vez más alta y el acceso a las herramientas de salud de la próxima década.

The past 10 years have been hailed as the decade of health.[1] The Millennium Development Goals, established in 2000, included health as a priority area for poverty alleviation.[2] In December 2001, the World Health Organization (WHO) Commission on Macroeconomics and Health convincingly showed that investing in health boosts economic development.[3] The Commission has been credited for helping to trigger a fivefold increase in funding for global health, from (US)$6 billion in 2000 to $30 billion in 2010.[4] Financial commitments were solidified in January 2002 with the creation of the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) following calls by then United Nations Secretary General Kofi Annan to establish "a war chest to fight the diseases of poverty."[5]

It was also 10 years ago, in November 2001, that members of the World Trade Organization adopted the Doha Declaration on the TRIPS (Trade-Related Aspects of Intellectual Property Rights) Agreement and Public Health amid fierce debates about the negative impact of trade rules on access to medicines. The declaration affirmed countries' sovereign right to protect public health when intellectual property stands in the way of access to medicines.[6]

Less noted but no less important was the founding roughly a decade ago of product development partnerships (PDPs) as not-for-profit entities to conduct and coordinate research and development into new drugs, diagnostics, or vaccines to address pressing health needs of resource-limited settings: the Medicines for Malaria Venture established in 1999, the Global Alliance for TB Drug Development (TB Alliance) in 2000, and the Drugs for Neglected Diseases initiative in 2003, to name a few. These new initiatives took drug development outside both industry and government.[7,8]

Three main factors lay behind these important, landscape-changing, political developments. First, the striking, unaddressed health needs for infectious diseases, and in particular human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS), sparked international civil society mobilization.[9] The Pretoria court case, in which a consortium of 39 pharmaceutical companies took the South African government to court over a law to improve access to antiretroviral medicines (ARVs), particularly exemplified the crisis in access to medicines in developing countries. Civil society mobilization in South Africa and elsewhere in the South, linking up with activists in the North, helped bring global attention to the problem and ultimately resulted in the withdrawal of the pharmaceutical industry lawsuit.[10]

Second, an effective system of producing affordable medicines was coming under threat, as trade agreements increasingly required ever tighter patent protection, including in developing countries with large generic manufacturing industries. HIV again served to exemplify the problem, with the annual cost of treatment with patent-protected ARVs reaching $10000.[10]

Third, political will emerged to challenge the systemic problem of neglected diseases research as the lack of a profitable market for diseases primarily affecting people in developing countries meant that research and development had come to a standstill in previous decades. An analysis found that only 1% of the new medications developed between 1975 and 1999 were treatments for tuberculosis (TB) and tropical diseases, despite these diseases causing 11% of the global disease burden.[11] The most commonly used tools for tuberculosis diagnosis remained unchanged for more than a century, and the most recent treatments were developed from the 1940s to the 1960s.[12]

This article discusses key developments in improving access to medicines for the big 3 killer infectious diseases: HIV, TB, and malaria; the role the initiatives launched 10 years ago have played to address them; and the challenges that lie ahead.

HIV/AIDS

Thirty-four million people are living with HIV today, more than ever before. But during the last decades, new infections were reduced from 3.1 to 2.7 million and AIDS deaths from 2 to 1.8 million per year.[13]

Ten years ago, just a few thousand patients were on antiretroviral treatment (ART) in developing countries, a number that has now reached more than 6.6 million.[13] Though this is a major achievement that seemed unthinkable 10 years ago, it still means that only half of those in need today have access to treatment.

A decade ago, ART was considered too expensive and too complex for developing countries. The considerable decrease in the price of HIV medicines driven by generic competition—from $10 000 per patient per year a decade ago to $61 today[14]—the simplification of drug regimens and monitoring needs, and the elaboration of strategies to simplify treatment provision and overcome human resources shortages by shifting medical tasks away from doctors to other healthcare workers were all key to breaking the deadlock. Civil society mobilization played an essential role in each of these aspects.[15]

Substantial international political commitment and funding was necessary as countries suffering from the world's highest burden of HIV could not have afforded the resources necessary to drive an appropriate response alone. The GFATM is widely recognized as one of two main funding mechanisms that have helped countries to increase prevention of HIV, TB, and malaria and expand treatment of and care for people with those diseases and is an example of what can be achieved through international solidarity with a clear focus on patients. GFATM ensured ART for 3.3 million people by the end of 2011 alone and aims to support 7.3 million by 2016.[16] The US President's Emergency Plan for AIDS Relief, launched in 2003, is the second important pillar of international support to AIDS prevention and treatment, supporting 3.9 million people on ART by the end of September 2011 and with a new target of 6 million people on treatment by the end of 2013.[17]

Until now, GFATM has been unique in adopting a "demand-driven" approach that relies on mobilizing sufficient resources to support all reasonable proposals for funding from affected countries. Proposals prepared at country level by Country Coordinating Mechanisms bringing together representatives from government, aid agencies, and non-governmental organizations, and people living with the diseases have promoted local ownership and participatory decision making in determining needs and overseeing implementation. Yet despite an impressive track record, the GFATM faces significant financial shortfalls, forcing it to cancel for the first time in its 10-year history its annual funding round.[17] Affected countries now effectively have no new funding opportunities until 2014. Though a transition mechanism is being put in place to prevent interruption of programs, the funding crisis will significantly slow the expansion of life-saving treatment for the 3 diseases. It will also make it hard to make important improvements in the quality of care through, for example, earlier initiation of ART and better treatment regimens and monitoring.

Decreased financial support for global health in general, and HIV/AIDS in particular, occurs despite political commitments to have 15 million people on treatment by 2015[19] and at a time when there is evidence that the epidemic can be reversed. A landmark study in 2011 showed that ART not only reduces mortality and morbidity but also can substantially reduce HIV transmission.[20] This makes ART provision the most effective biomedical prevention tool for HIV/AIDS we currently have[21] and means that scaling up ART access makes good financial sense as well.[22]

With funding for AIDS decreasing,[13] ensuring that medicines remain affordable is as important as ever. But all key generic-producing countries including India (which supplies more than 80% of ARVs in developing countries[23]), China, and Brazil protect patents, so generic production of new medicines generally is blocked.

Newer ARVs, such as raltegravir and etravirine, to which patients will eventually need to switch, exist only as originator products and cost (US)$675 and (US)$913 per year, respectively (to which the price of 2 or more other drugs need to be added to form a complete treatment regimen).[14] Unless these prices are reduced, treatment providers are effectively facing a treatment time bomb, as more and more patients will need to be switched to more expensive regimens.[24]

TUBERCULOSIS

For most of the past decade, AIDS has been fuelling the TB epidemic in Africa, and TB remains the second leading cause of death from an infectious disease after HIV, with up to 1.5 million deaths per year. Progress in bringing TB under control has been slow, and global TB incidence only started decreasing modestly in 2006.[25]

The GFATM has played an important role, having funded 8.6 million TB treatments since its inception and providing about $0.5 billion per year, mainly to the poorest countries. With an affordable treatment regimen and the biggest health burden in some of the emerging economies like China and India, TB control may at first sight seem less vulnerable to dwindling international support than HIV, with 86% of financing coming from the high-burden countries themselves.[25]

Yet countries are struggling with the growing and costly challenge of multidrug-resistant (MDR) and extensively drug-resistant TB,[26] as the usefulness of the WHO-recommended 6-month treatment regimen becomes increasingly limited. The number of MDR-TB cases is growing every year in Eastern Europe, Central Asia, and Africa, with Belarus currently topping the list with 26% of new TB cases and 60% of retreatment cases being MDR-TB.[25]

Considerable efforts by civil society organizations helped make MDR-TB a public health priority. As with HIV, it required challenging notions that MDR-TB was untreatable in resource-limited settings and that it would divert attention and resources from treating

drug-susceptible TB.[27] Although MDR-TB is now an international priority with an agreed-upon global plan to universal access to treatment,[28] too little practical progress has been made over the last decade. Only 46 000 people are diagnosed and treated out of an estimated 440 000 new cases every year.[25]

The cost of second-line drugs remains high at around $4500 on average per patient. Currently, the DR-TB drug market is too small and fragmented and barely attracts manufacturers. Price reductions from economies of scale will be realized only when more patients are put on treatment, but the vicious circle of high costs dissuading countries from addressing MDR-TB—meaning limited patient numbers keep prices high—needs to be overcome.[29]

The complexity of treatment is an additional barrier to scale up. Diagnosis is complex and expensive and even in high-prevalence settings is not yet routinely offered. A new automated molecular test offers a much faster diagnosis but costs $17 per test. In addition, to obtain an individualized picture of drug resistance and determine treatment options, full culture and drug sensitivity testing are still required.[30] MDR-TB treatment lasts for 18 to 24 months and is highly complex, with drugs inducing many side effects. As a result, treatment outcomes are poor (around 60% treatment success) and defaulter rates high.[31] Nevertheless, it has been demonstrated that good outcomes can be achieved in resource-limited settings supported by clinical or community-based models.[32,33] Despite the difficulties, treatment expansion is feasible.

But the financial situation of the GFATM is threatening initiatives to expand treatment for MDR-TB. Some high-burden countries that finally recognize the severity of the problem may be able to finance at least part of the response with their own resources: India, which produces a quarter of the world's MDR-TB cases, plans to diagnose and treat 30 000 new patients per year by 2014.

Improving the treatment regimen to make it more efficacious, of shorter duration, and more affordable will be an essential part of the path toward rapid and large expansion of MDR-TB treatment. Though the problem of drug resistance has been driven by irrational drug use and prescribing, with over-the-counter availability of TB drugs in many countries (which remains unaddressed), it also has been a predictable crisis, as no new TB drugs have reached the market since the 1960s.

Three PDPs were founded to address the research gaps in TB: the Global Alliance for TB drug development, the Foundation for Innovative New Diagnostics, and Aeras, for vaccines. In addition, some drug companies have restarted limited investment into TB drug development, often as a goodwill gesture. After decades of inactivity, there is again a pipeline of TB drugs in development, although this pipeline is not nearly as robust as those for more profitable diseases.[12]

Two new drugs, bedaquiline and delamanid, are the most advanced in clinical development. Both are being tested in MDR-TB patients, and approval by the US Food and Drug Administration is expected as early as 2012. However, additional studies will be needed not only to add these drugs to existing regimens but also to determine if a better and shorter regimen for MDR-TB can be defined, removing at least some of the old drugs. There is so far insufficient interest in and funding for such studies and few research sites with adequate capacity to carry them out.

Market introduction of the new drugs is another challenge: they should be available to all those in need but only through appropriate programs and adequately skilled health workers in order to avoid the rapid development of resistance. Price should not be a barrier and should not be used as a way to restrict use.

Ultimately, a completely new regimen, effective against both current drug-sensitive and drug-resistant TB, is needed. This still is some way off, at least for a universal regimen that will not require sophisticated tests before treatment can be started.

MALARIA

Progress in malaria control over the past decade has been significant. Global malaria incidence decreased by 17% and malaria-specific mortality by 26% since 2000. Yet malaria still takes a heavy toll, with an estimated 216 million episodes of malaria and 655 000 deaths occurring in 2010. Of these, 91%were in Africa, and 86% of global malaria deaths were in children under 5 years of age.[34] More recent estimates suggest that the disease burden is even higher, putting the number of deaths from malaria in 2010 at 1.24 million.[35]

Three tools were the essential ingredients of progress during the past decade: artemisinin-based combination therapies (ACTs), impregnated bednets (including long-lasting insecticide-treated nets), and malaria rapid diagnostic tests (RDTs), which enable the confirmation of malaria even in the most remote areas where microscopy is not available.[36]

Artemisinin, a natural compound of *Artemisia annua*, an herb described as "a true gift from old Chinese medicine," has been used as a traditional treatment for malaria and fever for more than 2 millennia and became more widely recognized and studied in the 1960s to 1990s.[37] WHO first stated that ACTs should be introduced in 2001, after studies had long shown widespread and high-level resistance to the older drugs and in particular choloroquine, which has been in use since the 1940s.[38] It took repeated, often redundant resistance studies in many countries and much mobilization over the following years to convince African governments to change national protocols.[39]

From the beginning, with ACTs being considerably more expensive than older, increasingly ineffective treatments such as chloroquine and sulfadoxine-pyrimethamine, cost was a major barrier. With international funding necessary for their large-scale introduction, the GFATM became the main funding source, supporting 230 million malaria treatments to date. Since 2005, the

US President's Malaria Initiative (PMI) has acted as a second pillar of international support to malaria control.

In parallel, important price reductions were achieved thanks to generic competition. In 2001, WHO negotiated an agreement with Novartis (Basel, Switzerland), the manufacturer of one of the main ACT treatments, to lower the cost the company was charging the public sector from $4 to $2.40 per adult treatment. The company at the time claimed that $2.40 was its cost, implying it could go no lower. But competition from multiple producers has since lowered the price to under $1, illustrating again how market competition acts as a greater catalyst to price reductions than negotiated discounts with pharmaceutical companies.[40]

Reducing the price of ACTs until they reach a level similar to the average chloroquine price of less than $0.10 will not be feasible, as the production of the raw material through plant extraction is too costly. A semisynthetic artemisinin will reach the market in 2012 but with limited production capacity and only modest cost advantages initially.[41]

A scheme was developed in 2004 to subsidize the cost of ACTs in order to make the medicines more affordable in the private sector. This concept is currently being piloted through the Affordable Medicine Facility—malaria (AMFm) in 7 countries, starting in 2011.[42] Many questions remain about the scheme. Mark-ups by middlemen add significantly to the end price, and some question whether scarce donor money shouldn't be used to expand access to free care through the public sector rather than subsidizing the private sector, particularly given the funding crisis currently affecting global health. The AMFm got off to a troubled start as it allowed orders from wholesalers to increase so rapidly that they disrupted the global raw material market, contributing to a tripling of the raw material price in 2011.[43]

More recently, WHO also has changed its recommendations to countries for the treatment of severe malaria—from quinine injections to injectable artesunate. Severe malaria occurs less frequently than uncomplicated malaria but is often fatal. Injectable artesunate is safer and easier to use, and it reduces mortality by 39% in adults and 24% in children, compared to quinine.[44] It is also more expensive, but a global treatment switch would only cost an additional $31.8 million per year—a small investment within the billion dollar budgets of the GFATM and PMI even in the current financial climate.[45]

After initial difficulties, the uptake of ACTs has been encouraging in the last 5 years, with annual sales of ACTs approximately matching the annual number of malaria cases. But the concern remains that malaria treatments are still widely used based on fever symptoms alone. As diagnosis is not always confirmed through microscopy or the use of RDTs, there is significant overtreatment. An increased use of RDTs to confirm malaria diagnosis is needed as is now recommended by WHO.[46]

The emergence of drug resistance is a threat because of the continued availability of artesunate monotherapy, low-quality drugs and potentially because of overuse (as with chloroquine previously). Suspected resistance to artemisinin has now been identified in 4 countries in Southeast Asia.[34] It would be a tragedy to lose "the gift of Chinese medicine" within a couple of decades of WHO's recommending its introduction and after it has been used for millennia.

It will also be very hard to replace. Malaria drug research has been revived through the product development partnership's Medicines for Malaria Venture, but most of the drugs in the pipeline are artemisinin-like molecules, and a different drug class is at least 5 years away.

Ambitious targets have been set to eliminate malaria in a range of countries.[36] This may be feasible in all but the countries with the highest transmission rates. It seems more urgent, therefore, to control malaria and reduce deaths in the 42 countries in Africa that are not ready yet for elimination.

LOOKING TO THE NEXT DECADE

The past decade has been a golden decade for global health, driven by strong international mobilization and political will to address priority health problems of the poorest. It has resulted in significant progress in expanding access to treatment and reducing mortality from and incidence of the main infectious diseases. Nevertheless, major needs remain, including those outlined below.

Competing Health Priorities

The "vertical" approach to HIV, TB, and malaria is criticized by some as a distraction from the need to support health systems more broadly or by those who contend that the scope of the GFATM should be expanded; for example, to finance the health-related Millennium Development Goals.[47,48] Other health challenges such as mother and child health received comparatively less investment. However, one of the strengths of the GFATM has been its clear focus on patients and its prioritization of 3 diseases. Whatever approach is adopted as a means to address a broader set of health priorities in an integrated way, it will need to build on, and not backpedal on, the progress being made for major infectious diseases.

Shifting Burdens of Disease

Additional health challenges have increased in importance during the past decade: many developing countries now face the double burden of infectious diseases and noncommunicable diseases. Addressing noncommunicable diseases will require both a focus on prevention and basic interventions but also the access to treatment for complex diseases including cancers. Policy discussions have so far only focused on the first; lessons need to be learned from HIV, another chronic disease, from the past decade.[49]

Dwindling Political Attention and Financial Shortfalls

Current financing is insufficient to even adequately address HIV, TB, and malaria, and there is a risk of backtracking on progress. International funding for global health has become more difficult to mobilize, and the time of large financial commitments made at annual G8 meetings is over. The financial crisis has made the leading economies more inward looking. Affected countries need to increase their investment in health, but the need for global solidarity will not go away. Major emerging countries like Brazil, Russia, India, China, and South Africa (collectively called the "BRICS") do not appear ready to become significant international donors. The health challenges in BRICS countries are significant, and they are only just being weaned off international donor support. Least-developed countries have exceeded in total health expenditure the recommendations of the Macroeconomics and Health Commission (personal communication with Dr David Evans, World Health Organization, December 16, 2011). Significant additional and predictable funding for global health solidarity is therefore needed. An example of how innovative financing can benefit health already exists: a tax on airline tickets implemented by France and a number of other countries generates revenues that flow to UNITAID, a multilateral organization that funds medicines and diagnostics for HIV, TB, and malaria.[50] Additional resources could be generated by creating a financial transaction tax (FTT), such as the one currently being debated in Europe, and dedicating a portion of the proceeds to healthcare.[51] As the idea of a Eurozone FTT becomes a firmer political possibility, no leaders have yet committed a portion of the expected revenue to support global health.

Increasing Difficulties in Producing and Providing Access to Affordable Medicines

Increased intellectual property protection that prevents production of newer medicines in key generic-producing countries such as India, Brazil, and China will continue to be fiercely debated in the coming decade. In the future, it should be assumed that all new medicines that are true innovations (and not minor modifications to existing drugs) will be widely patented.

The need to ensure affordability will require political will to enforce strict patentability criteria, allow for patent opposition, routinely issue compulsory licenses, and resist pressure by rich countries to further increase monopoly protections. Although the Doha Declaration continues to play an important role, it is increasingly being eroded. Under international trade regulations, countries are free to determine patentability criteria or to issue compulsory licenses to overcome patents, but few countries have implemented these flexibilities into national legislation, and fewer still have made use of them—with the notable exception of India, Thailand and Brazil.[52] This is a reflection of the considerable political pressure from industry and rich countries not to use them.

A better balance between health and trade is needed as the importance of reining in drug costs becomes ever more acute. Increasingly, use of these flexibilities has been constrained through bilateral trade agreements. Both the European Union–India Free Trade Agreement and the European Free Trade Association-India deal currently being negotiated pose a threat to access to medicines by introducing, for example, intellectual property enforcement measures. The United States is negotiating the Transpacific Partnership Agreement with a number of Asian and Latin American countries, which it considers the blueprint for future US-led free trade agreements where significant threats to access to medicines exist.[53]

The overall trend is that a system of affordable medicine production for resource-limited countries is continuously eroding and nothing adequate is being proposed to replace it. Though health groups have been fighting a defensive battle to maintain the possibility of generic production for as long as possible, it may now be time to call for revision of the TRIPS Agreement itself to ensure that it is consistent with access to medicine as a key aspect of the right to health.

Evolving Strategies From Drug Companies

Pharmaceutical companies continue to affirm that concerns around the price of medicines can be resolved through tiered pricing policies—where developing countries are offered price discounts, with the least-developed countries paying the least. There is evidence, however, that lower-middle income countries are squeezed out of standardized price discounts and face increasing prices.[23] While tiered pricing reduces the cost burden, it is in most cases significantly less efficient than generic competition in reducing prices.[54]

Some patent-holding pharmaceutical companies have entered into voluntary license agreements to authorize generic manufacturers to produce generic versions of their medications. The terms of such licenses are typically secret and have many restrictions, on geographical scope in particular. Voluntary licenses can be part of the solution if they are used in a way that responds to medical needs, as pioneered by the recently created Medicines Patent Pool.[10] Experience with voluntary licenses to date is that companies will need to be under greater pressure before they allow access in all countries; the inherent limitation lies in the voluntary nature of this approach.

In addition, the decade ahead will see changes in the pharmaceutical industry—including Indian generic companies being bought by multinational companies and generic companies entering into research and development—that are of concern for the future capacity of generic competition for newer drugs. Profit expectations on one hand and access challenges on the other for noncommunicable diseases will likely crystallize the fight for access to medicines.

A Global Framework for Research and Development

A decade after the establishment of PDPs, there is today a range of products in the pipeline that can be expected to reach patients in the coming years. This is significant progress. But at the same time, PDPs are only a very limited effort to address large research and development needs not comparable to investments made into more profitable areas like cardiovascular diseases or even hepatitis C. The TB Alliance's goal to develop a completely new treatment regimen that works for all TB patients, for example, remains many years away. Beyond HIV, TB, and malaria and certain neglected tropical diseases, significant innovation needs remain unaddressed. The PDPs also face considerable funding challenges, with public funding having decreased since onset of the financial crises and philanthropic funding, on which the PDPs are still heavily dependent, not being easily expanded.[55]

Intense policy discussions have taken place at the intergovernmental level during the past decade recognizing that more systematic changes to the current research and development system are needed to ensure that research and development is driven toward major public health needs and the specific requirements of resource-limited settings and that its fruits are affordable.[56,57] A key concept that has emerged is a need to separate the cost of research and development from the price of products. This means that research and development should be funded with grants or innovation rewards (or prizes)[58] rather than relying on high prices protected by drug monopolies to recoup investments made into medical research and drug development. This separation would allow research and development to be steered toward areas of greatest medical need, and not only as in the current patent-driven model, toward areas of high commercial return. At the same time, such an approach would overcome the problem of high product prices that leads to the exclusion of patients who cannot afford them.

A WHO Consultative Expert Working Group on Research and Development: Financing and Coordination has further examined the available options and recommends to the World Health Assembly in May 2012 to start negotiation of a research and development convention as a binding legal instrument to ensure adequate funding toward agreed health priorities and access to the fruits of this research.[59]

This is the type of long-term solution that countries need to support to ensure that future innovation is driven in a way that it meets health needs, products are priced affordably, and the access to medicine struggles of the past decade are not condemned to be repeated.

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FEATURE

The NAFKAM International Registry of Exceptional Courses of Disease Related to the Use of Complementary and Alternative Medicine

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Norway, patient registry, NAFKAM, case reports, exceptional courses of disease, complementary and alternative medicine, CAM, medical assessments, safety

The increasing use of complementary and alternative medicine (CAM) represents a continuing demand for treatment approaches in parallel with, or as an alternative to, conventional healthcare delivery.[1,2] Some patients report considerable health improvements related to their use of CAM,[3-6] and others report no effect or possibly harm.[7] Limited efforts have been made so far to systematically collect patients' personal experiences with various CAM therapies. Methods to collect "best cases" after the use of CAM in cancer patients have been initiated in the United States and Germany.[5,8,9] The focus of these projects has been to assess treatment response on outcomes measured independently of the patients' awareness of, experience with, and reflections on things such as tumor size or survival.[6] They have either concentrated on one condition or have constituted a one-time limited research project. The National Research Center in Complementary and Alternative Medicine (NAFKAM) in Norway believes it is important to monitor positive as well as negative patient experiences after the use of CAM, and in 2002, the first international registry for long-term collection of exceptional "best" and "worst" cases was established. In the beginning, only severe and chronic diseases such as cancer, multiple sclerosis (MS), asthma and allergy, migraine, and chronic fatigue syndrome were included, but the registry has since been expanded to include all health conditions. The Registry of Exceptional Courses of Disease (hereafter referred to as "the Registry") serves as a basis for research on questionnaire data, medical assessments, and interview data from "exceptional" patients' experiences and reflections.[3,6]

GOALS

The purposes of the Registry are to (1) collect patient-reported experiences from courses of illness/disease that have followed a different course than expected; (2) make these patient experiences accessible to researchers in a searchable format; and (3) monitor the collected experiences and refer series of similar experiences to researchers and health authorities.

INFRASTRUCTURE

The Registry is located at NAFKAM's offices in Tromsø, Norway. NAFKAM is part of the Department of Community Medicine at the Faculty of Health Sciences, University of Tromsø. A steering committee has been established (2 researchers from NAFKAM and a representative from a national patient organization), and a 50% administrative position has been allocated to the day-to-day running of the Registry. The Registry is 100% funded by NAFKAM, which in turn is funded by the Norwegian Ministry of Health and Care Services.

Information about the Registry is available through the websites of NAFKAM and the Norwegian Information Center on Complementary and Alternative Medicine as well as the websites of a number of cooperating patient organizations throughout Scandinavia. Doctors, alternative practitioners, and the media also provide patients with information about the Registry. So far, no paid advertising has been used.

Data to be included in the Registry can only be submitted by the patient him- or herself or by close family (if the patient is a child or has passed away). The data are collected through a self-administered questionnaire (on paper) with both open and closed questions. Topics include demographic information, history of diseases, CAM and conventional treatments used, and reasons for the "exceptional" classification of the disease course. A request is made for informed consent for the use of the collected data for research purposes and consent for access to medical records from hospitals, general practitioners, and CAM providers. Some patients have attached letters, notes, books, etc.

Core information from the questionnaire is entered into a database at NAFKAM, and the whole questionnaire and the informed consent form are physically stored, along with medical records collected for some cases, in fireproof, locked filing cabinets at NAFKAM. The documents are also stored in portable document format for future retrieval. The database is placed as a part of EUTRO (an information technology solution designed to protect and manage biologic material, metadata, data, and projects for major health surveys) at the Department of Community Medicine. An overview of all available Registry variables can be found online (http://www2.uit.no/ikbViewer/page/ansatte/organisasjon/hjem?p_dimension_id=88112&p_menu=42374&p_lang=1).

Eligible Patients

To be included in the Registry, a patient must have (1) had a disease/health problem, (2) experienced unexpected improvement or worsening of the course of disease, and (3) related this improvement or worsening to the use of CAM. In the Registry, "exceptional courses