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PHOTO HANNEKE DE VRIES

ESSENTIAL MEDICINES

ACCESS, QUALITY AND RATIONAL USE

CONTENT

2 BILLION

Modern health care is unthinkable without the availability of necessary medicines. Yet, close to 1 in 3 global citizens – 2 billion people globally – do not have access to lifesaving and health-supporting medicines. This directly challenges the fundamental principle of health as a human right. The theme of the NVTG annual symposium on October 16th 2015 addresses this injustice and places essential medicines in the middle of the debate on achieving Universal Health Coverage. In parallel to the symposium theme, this edition of MT*b* looks at essential medicines from access, quality and rational use perspectives

Rewriting the rules is needed, as according to 't Hoen the current pharmaceutical system can't be justified because we fail to provide affordable medicines for the people and the communities that need them. Access to high priced medicine – currently a subject of fierce debate in the Netherlands [1] – is not only an issue for developed countries as seen in the assessment of Devalière et al., who compared prices of treatment for hepatitis C across Europe. Reforms of the research and development model and greater transparency may eventually avoid situations like the ones she found in Latvia. The problem also exists for other diseases and other low- and middle-income countries, as Ewen reports on poor insulin availability.

Both Ravinetto and Dorlo address the devastating effects of medicines that do not comply with quality specifications (substandards) and of products that are intentionally and fraudulently produced (falsified medicines). Where Ravinette explores ethical challenges from a public health perspective, Dorlo looks at the role of the poor quality of antimalarials in the emergence and spread of resistance against antimalarials.

Diseases that could easily be treated with antibiotics can become life-threatening again. In a post-antibiotics era, people would die of common infections. No, this is not science fiction. Rational use and prescription (focusing on the drivers of overuse, underuse or misuse of medicines) is the plea of Schippers, the Dutch Minister of Health, Welfare and Sports. It is expected that the Dutch government, during its EU presidency in 2016, will place antimicrobial/antibiotics resistance high on the political agenda.

The first model list of essential medicines was published in 1977. However, it took some years to come up with action plans to improve access to and use of medicines. The plans from decades ago are still relevant today according to Hans Hogerzeil, professor Global Health and chair of the Lancet Commission on Essential Medicines Policies. Still, the proportion of the population without access to a basic range of affordable essential medicines of assured quality is large - very large - as if decades have passed without any progress.

Of course that is not completely the case. Let positive examples guide us. It was not free-market forces which led to a 99% (!) decrease in the price of antiretroviral medicines. It was concerted international action that made this possible. Let's consider this an example of how to deal with the long list of (new) essential medicines waiting to become affordable for those in need of treatment.

ESTHER JURGENS AND JOOST COMMANDEUR, EDITORS THIS MT*b*

1. Summer 2015: health insurers and hospitals are requesting the Minister to establish a fund for high-cost medicines

JOSEPH SOHM / SHUTTERSTOCK.COM

Access to Essential Medicines in support of Universal Health Coverage

THE NVTG ANNUAL CONFERENCE ON OCTOBER 16, 2015 WILL BE DEDICATED TO THE CONTRIBUTION OF ESSENTIAL MEDICINES TOWARDS ACHIEVING UNIVERSAL HEALTH COVERAGE. **HANS HOGERZEIL**, FORMER WHO DIRECTOR FOR ESSENTIAL MEDICINES AND PHARMACEUTICAL POLICIES AND CURRENTLY CO-CHAIR OF THE LANCET COMMISSION ON ESSENTIAL MEDICINES POLICIES, PRESENTS AN OUTLINE OF THE ISSUES AT STAKE AND THE CHALLENGES FOR THE FUTURE.

HIV/AIDS medication Community Rehabilitation Programme. Nairobi, Kenya.

Access to essential medicines is a crucial condition for addressing the most important global health challenges, such as child survival, maternal mortality, HIV/AIDS, tuberculosis, malaria and the growing global epidemic of non-communicable diseases.

Access to essential medicines is therefore also widely recognized as part of the progressive realization of human rights. The International Covenant on Economic, Social and Cultural Rights of 1966, now ratified by over 160 countries, specifically mentions access to health care goods and services as part of the fundamental right to the highest

attainable standard of health (i.e. the right to health). [1] The authoritative General Comment 14 of the Commission on Economic, Cultural and Social Rights of 2000 specifies that the right to goods and services includes essential medicines 'as defined by the WHO Action Programme on Essential Medicines'. [2] Numerous national court cases have further confirmed these rights for individual patients or patient groups. [3]

The first World Health Organization (WHO) Model List of Essential Medicines was issued in 1977. However, the international essential medicines movement really started in 1985. In that year, around 200 government officials and experts from over 50 countries met in Nairobi to discuss an action plan to improve the use of medicines worldwide. According to Halfdan Mahler, director-general of the WHO at the time, the meeting was 'a historical landmark in the evolution of the action required to ensure that drugs are used more rationally throughout the world'. This remains the only global conference to date where government officials and independent experts were specifically convened to discuss essential medicines policies.

The results of the Nairobi conference were adopted by the World Health Assembly in 1986. This triggered a series of actions to improve access to and use of medicines that are still relevant today: (1) international guidelines to develop national pharmaceutical policies, (2) programmes to strengthen regulatory authorities, (3) teaching materials for health care professionals, (4) good procurement and distribution practices, and (5) global standards for information about medicines. By the turn of the century, 156 countries had defined a national list of essential medicines. After 2000, the concept of essential medicines also proved to be a critical element towards achieving the health-related Millennium Development Goals. Medicines and vaccines have been key to the eradication of diseases (small pox and polio), the mitigation of pandemics (HIV/AIDS, tuberculosis and malaria) and the reduction of maternal and child mortality.

FUTURE DIRECTIONS

Essential medicines will remain important in the future as well. The discussions on the post-2015 development goals and the 30th anniversary of the Nairobi conference in November 2015 provide an opportunity to raise awareness of the global relevance of the essential medicine concept, and to update the needs for further operational research to improve the effectiveness and efficiency of essential medicines policies and programmes.

It is against this background that in 2014 The Lancet established a Lancet Commission on Essential Medicine Policies[4] to take stock of what has been learned over the last 30 years and to use new insights for the effective implementation of the new Sustainable Development Goals (SDG). The Commission report, which is expected in 2016, will use as its framework the new SDG and its medicine-related targets (See box).

Medicine-related Sustainable Development Goals (draft May 2015)

SDG 3.8: Achieve universal health coverage (UHC), including financial risk protection, access to quality essential health care services, and access to safe, effective, quality, and affordable essential medicines and vaccines for all.

SDG 3.b: Support research and development of vaccines and medicines for the communicable and non-communicable diseases that primarily affect developing countries, provide access to affordable essential medicines and vaccines, in accordance with the Doha Declaration which affirms the right of developing countries to use to the full the provisions in the TRIPS agreement regarding flexibilities to protect public health and, in particular, provide access to medicines for all.

These two SDGs reflect the two most important challenges in national medicine policies: (1) to ensure equitable access to essential medicines as part of universal health care and the ful-

filment of the right to health; and (2) to promote research and development of missing essential medicines and ensure their availability (physical and financial) to all who need them.

EQUITABLE ACCESS TO BASIC ESSENTIAL MEDICINES

Exact estimates are difficult, but the best guesses remain that in many very low and low income countries about a third of the population has no regular access to a basic range of affordable essential medicines of assured quality. In some areas, this figure can be as much as half the population. Indeed, a house-hold survey in Uganda showed that a third of the people interviewed had never been able to get the medicines they were prescribed the last time they consulted a health worker. [5]

Very detailed WHO Service Availability and Readiness Assessments surveys have also shown that a large proportion of rural clinics miss several key medicines for maternal health, such as oral and injectable contraceptives, oxytocin, misoprostol and magnesium sulphate. It is clear that, without such medicines, reproductive care is simply not possible. These and other data support earlier estimates that between one and two billion people have no access to basic essential medicines yet. It should be mentioned here that only one-third of the 1.4 billion global poor live in least–developed countries; two-thirds are now found in the lower economic strata of middle-income countries. Inequity between countries is gradually being replaced by inequity within countries.

EQUITABLE ACCESS TO NEW ESSENTIAL MEDICINES

New essential medicines are expensive, as the case of antiretroviral medicines (ARVs) has shown. Originally they were priced at over USD 10,000 per person per year. WHO classification as an essential medicine in 2002, international advocacy and action by NGOs, generic production of fixed-dose combinations in India, the WHO/UN prequalification programme, and large-scale public funding through the Global Fund, the United States President's Emergency Plan for AIDS Relief (PEPFAR) and UNITAID have achieved a 99% price reduction. The current first-level regimens now cost less than USD 80 per person per year. This was not the result of free market forces but of concerted international action. The 100-fold price differential between originator price and final generic price is in line with a similar ratio that has been in existence for 40 years for standard childhood vaccines and oral contraceptives. However, the situation is very different for second-line ARVs and new medicines for tuberculosis. Here the prices can still be very high, especially in middle-income countries, because of new patent legislation demanded through the World Trade Organization and bilateral trade agreements like the TRIPS Agreement. Several new essential medicines are now where the first-line ARVs were in 2002. In April of this year, the WHO added 20 medicines for common and treatable cancers to the latest Model List of Essential Medicines. Many of these medicines are still under patent and most will be out of reach for most patients in low- and middle-income countries. Yet this listing is a very important first step, as it implies that these medicines will now have to be made affordable to all who need them.

CONCLUSION

As demonstrated by the case of ARVs, free market forces will never achieve universal access to medicine for the poor. Concerted government action is needed to make all medicines from the latest Model List of Essential Medicines available for all patients who need them, at a price the patients and the community can afford. The practical application of human rights is increasingly being used by governments as a framework for promoting equity and achieving the new sustainable development goals.

HANS V. HOGERZEIL, MD, PHD, FRCP EDIN
PROFESSOR OF GLOBAL HEALTH AND THE RIGHT TO HEALTH, UNIVERSITY MEDICAL CENTRE, GRONINGEN, THE NETHERLANDS
H.V.HOGERZEIL@UMCG.NL

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Access to essential medicines and intellectual property – Is it time to rewrite the rules?

In the late nineties, the magnitude of the AIDS crisis drew attention to the fact that millions of people in the developing world did not have access to the medicines they needed to treat disease or alleviate suffering. In 2000, only one in a thousand people living with HIV in Africa had access to treatment. Highly active antiretroviral treatment (HAART) was available in wealthy countries and had changed AIDS from a death sentence into a manageable chronic disease. But the drugs (ARVs) were available only from originator companies, who controlled the patents. They produced small quantities carrying paralysing price tags of USD 10,000 to USD 15,000 per person per year.

The high cost of HIV medicines focused attention on the relationship between patent protection and high drug prices. [1] The difficulties developing countries experienced in paying for new essential medicines needed to treat the millions of people that were dying of AIDS raised concerns about medical patents.

It is ironic that the access to HIV medicines crisis hit just after countries had agreed to the 1994 World Trade Organization (WTO) Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS), which sets out global minimum standards for the protection of intellectual property (IP). The TRIPS Agreement obligated all WTO member countries to grant patents with a minimum of 20 years duration and to grant patents in all fields of technology, making it impossible to exclude medicines and food from patenting.

The global mobilization around HIV led to the introduction of a number of IP related mechanisms, some of which were contained in the 2001 WTO Doha Declaration on TRIPS and Public Health, to bring down the price of antiretroviral medicines. [2] These mechanisms include the use of flexibilities in TRIPS, the delay of medicine patent enforcement for least developed countries, the introduction of strict patentability criteria to limit the number of patents granted and to prevent 'ever-greening' of patents, and in 2010 the establishment of the Medicines Patent Pool, a United Nations backed initiative that negotiates patent licences to enable generic producers to make and sell affordable versions of HIV medicines. Today, first-line ARV regimens are available from generic suppliers for USD 95 to USD 158 per person per year, [3] a sharp decrease from the USD 10,000 to USD 15,000 of a decade and a half ago.

Whether these mechanisms to reduce medicine prices will also be applied to increase access to new essential medicines remains an open question. In May 2015, the World Health Organization added several important medicines, [4] including medicines for the treatment of cancer, tuberculosis and hepatitis C, to its Model List of Essential Medicines (EML). The uniqueness of these medicines - aside from their value as treatments for devastating illnesses - lies in their high price. Now that the WHO has given these medicines the status of "essential", they must be made both available and affordable. As innovative new medicines are increasingly patented around the world and thus only available at monopoly prices that prevent widespread access, a public policy response is needed to address the intellectual property challenges associated with essential treatments. Perhaps it is time for an essential medicines patent pool to ensure that the generic production of all WHO essential medicines can take place.

High drug pricing is justified by the pharmaceutical industry as compensation for the cost of research and development (R&D) of new drugs. Without patents, they argue, pharmaceutical R&D will come to a standstill. Commercial companies will indeed not invest in the development of a new product if it cannot generate significant profits. The huge profits sustained by the patent system, however. affect priority setting in R&D by companies. Companies do not consider it profitable to invest in the development of medicines for people with limited or no purchasing power. The situation with regard to the neglected diseases crisis, first described by Médecins sans Frontières in its 2001 seminal report 'Fatal Imbalance: The Crisis in R&D for Neglected Diseases' [5], is still much the same today despite the globalization of stronger intellectual property protection. [6] Although there have been several new R&D initiatives launched over the past 10-15 years, progress has been incremental, for example in the field of neglected tropical diseases (NTDs) and based on not-for-profit initiatives.

The lack of medical innovation and the lack of access to health tools (including medicines, diagnostics, and vaccines) to address global health needs are now well-documented and widely recognized. The industry also recognizes that the current innovation system is detrimental to dealing with global health needs. For example, in response

to questions about the role of the pharmaceutical industry in dealing with the Ebola outbreak in West-Africa, Andrew Hollingsworth, policy manager of the Association of the British Pharmaceutical Industry, said, 'Unfortunately, the standard economic model for drug development, in which industry takes all of the risk in R&D and gets a return on investment from successful products, does not work for diseases that primarily impact low-income countries and developing healthcare systems.' [7]

In 1958, the economist Fritz Machlup wrote about the patent system, 'If we did not have a patent system, it would be irresponsible, on the basis of our present knowledge of its economic consequences, to recommend instituting one. But since we have had a patent system for a long time, it would be irresponsible, on the basis of our present knowledge, to recommend abolishing it.' [8]

No one is suggesting the abolition of the patent system. However, based on today's knowledge of the challenges for both access to and innovation of the current pharmaceutical development system, we urgently need to look at alternatives. We need a mechanism to bring the price of new essential medicines down so they become affordable to the people and the communities that need them. One could imagine an essential medicines patent pool to make that happen. Equally important is ensuring that research and development for new essential treatments takes place. New financing models for R&D need to provide the correct incentives for innovation while keeping drug prices low. Such models should be based on delinkage principles in which the cost of R&D is delinked from the price, in other words innovation that is no longer dependent on the ability to charge high prices. [9] At its assembly in 2016, the WHO will consider recommendations for an international medical R&D treaty made by a group of experts convened by the WHO in 2012 to better prioritise R&D projects and share the cost of such R&D. [10, 11] These international talks provide an opportunity for the medical community to step up engagement with an issue that for too long has been the exclusive domain of trade, business and IP experts and to rewrite the rules so that much needed innovations in health care can be financed and are accessible to all in need of them.

ELLEN 'T HOEN, MEDICINES LAW & POLICY, LLM
ELLENTHOEN@MEDICINESLAWANDPOLICY.NET

'WE NEED A MECHANISM TO BRING THE PRICE OF NEW ESSENTIAL MEDICINES DOWN SO THEY BECOME AFFORDABLE TO THE PEOPLE AND THE COMMUNITIES THAT NEED THEM. ONE COULD IMAGINE AN ESSENTIAL MEDICINES PATENT POOL TO MAKE THAT HAPPEN'

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Access to high-priced new medicines: an increasing burden for government health budgets

The recent inclusion of high-priced patented cancer medicines on the World Health Organization (WHO) Model List of Essential Medicines (EML) has changed the landscape for access to essential medicines as a human right. Even wealthy governments in the North are struggling with the paradox that whilst some new medicines are considered essential (i.e., they have been judged to provide significant therapeutic advantage by the EML expert committee), they are also unaffordable. In low- and middle-income countries (LMICs) the situation is even worse. Whilst essential treatments should be made available, the burden on governments and on the patient, who generally has to (co)pay for treatment, means they are simply out of reach. This paper takes the example of sofosbuvir (Sovaldi®) in Europe, an on-patent essential treatment for hepatitis C, which was added to the EML list in April 2015, to examine price differences between countries.

ASSESSING ACCESS TO MEDICINES

The current model of equal access to medication for patients throughout Europe is becoming unsustainable. Demand for treatments is increasing, mainly due to an ageing population, the growing chronic disease burden and new developments, such as personalized medicines and technologies[1].

At the same time, the price of new medicines is rising rapidly. High demand is therefore compounded and exacerbated by high medicine prices. For example, expenditure on pharmaceutical treatments in EU countries rose by approximately 76% between 2000 and 2009[2] and remains a grave concern across the EU[3]. This poses a massive burden on health systems, already compromised by the recent economic crisis[4].

Through quantitative and qualitative research, the two main dimensions of access to medicines, affordability and availability*(1)*, were assessed in four European countries: Spain, France, Austria and Latvia. Official hospital prices of five selected medicines were related to national gross domestic products (GDP) per capita and purchasing power parity (PPP) to assess affordability. Semi-structured interviews with key informants from each country were conducted to gather information on availability and affordability of the selected medicines for the in-patient sector.*(2)*

Approximately 130 to 150 million people suffer from chronic hepatitis C infection worldwide. Approximately 500,000 people die each year from hepatitis C-related liver diseases[5]. In 2012, more than 30,000 cases of hepatitis C were reported in 27 EU countries[6]. Amongst the treatments recently available on the market, sofosbuvir, marketed by Gilead as Sovaldi®, was granted a marketing authorization valid throughout the EU in January 2014[7].

Having collected the unit prices*(3)* in the four selected countries, data were analysed, compared in nominal value*(4)* and adjusted by the countries' purchasing power parity (PPP) to ensure that the prices of medicines are valued similarly and provide an affordability estimate. The PPP adjusted price was calculated by using the PPP conversion factor from Eurostat (2013). The table below shows the price differences between the EU Member States. Latvia, although having the lowest annual GDP per capita, is paying the highest price for sofosbuvir.

GOVERNMENT'S RESPONSES

Sofosbuvir is not on the list of medicines that are reimbursed by the state insurance scheme in Latvia. In the interviews, informants blamed the lack of government-sponsored access on its unaffordable and very high price. Therefore, patients are forced to cover costs for the treatment themselves out-of-pocket.

Sofosbuvir is reimbursed, however, in Austria, France and Spain, albeit on a case-by-case 'restricted procedure' basis. A restricted procedure means that patients must fulfil defined country-specific clinical eligibility criteria to obtain treatment reimbursement. Interview respondents confirmed the considerable contrast of the hospital availability and reimbursement status of high-priced medicines between Latvia and the other countries.

In all the countries studied, the lack of price transparency and collaborative efforts for procurement, in particular between the out-patient and in-patient sector (hospitals and pharmacies),

Table 1

Official hospital list price of Sovaldi in Euros. Unit price corresponds to the price of one oral pill application. Price per treatment corresponds to one pill per day over 12 weeks.

Country	GDP	Strength	Unit Price per pill	Price per treatment	PPP conversion factor	GDP/price ratio
Austria	38,100	400 mg	488.10	41 000.4	1.11761	1.28%
France	32,100	400 mg	488.11	41 001.24	1.13105	1.52%
Latvia	11,600	400 mg	733.02	61 573.68	0.679363	6.32%
Spain	22,500	400 mg	465.12	39 070.08	0.900630	2.07%

Source: GDP, PPP conversion factor data from 2014, Eurostat. Price data surveyed by the authors as of May 2015.

were repeatedly highlighted by interview respondents as posing a barrier to access.

CONCLUSIONS

Overall, national strategies to lower prices for medicines were perceived by informants as insufficient and not tackling core issues, such as the need to increase price transparency and improve cooperation in the management of hospital procurement. The in-patient sector still represents a black box for policy makers in that it remains unknown what hospitals pay for the medicines they purchase.

The lack of transparency on hospital prices, actual transaction costs and consumption can increase difficulties for governments to respond appropriately to increasing costs for medicines and to the public health needs of their population. The example of sofosbuvir reflects the increasing issue of unaffordability of medicines for European countries. To tackle this issue, which is expected to be no different in low- and middle- income countries, increased transparency for prices of medicines in the in-patient sector is needed. Therefore, hospitals' pharmaceutical expenditure and consumption at national and international levels should be surveyed. National and EU strategies to ensure equal access to high-priced medicines also need to be developed.

DISCUSSION

As this review implies, the pharmaceutical industry acts according to its own strategy, which results in significant prices differences between member states (tiered pricing). These price inequalities do not reflect any rational financial constraints on the health systems, since the member state with the highest procurement price (Latvia) has the lowest GDP.

The pharmaceutical industry justifies its high prices by claiming it makes large investment in research and development (R&D), but the truth is that no one knows how much is spent on the development of a new drug, and estimates by the industry and independent analysts vary greatly.[8, 9] In any case, R&D costs should not be the major driver when it comes to pricing(5). The added value that the medicine brings to patients and healthcare systems should also be taken into account. The issue of transparency is core here, as citizens have a right to know what public money is being spent on.

At the international level, the harmonized standard of intellectual property protection laid down in the Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) permits EU member states to issue a compulsory license to ensure affordable access to medicines for their citizens[10]. By issuing a compulsory license, a government authorizes the production and marketing of a cheaper generic version or versions of a patented medicine on the condition that authorized generic firms pay a license fee to the patent holder. A compulsory

license, or even the mere threat of issuing one, may result in a substantial decrease in the price of a medicine.

The recent patent opposition of Sovaldi®by Médecins du Monde in France paves the way to another policy option. By breaking the monopoly situation, generic competition has proven to be an effective way of lowering medicine prices and delinking the price of a medicine from its R&D costs.

In addition to the urgent short-term need to address the high cost of medicines, deep reforms of the R&D model and greater transparency are needed to respond to the global challenge of access to medicines from a long-term perspective. A strong political commitment is, however, a prerequisite.

DEVALIÈRE ALIÉNOR
EUROPEAN POLICY ADVISOR, HEALTH ACTION INTERNATIONAL
ALIENOR@HAIWEB.ORG

KATHARINA HAWLIK, MD, MSC.
GLOBAL HEALTH CANDIDATE, VRIJE UNIVERSITEIT
KATHIHAWLIK@GMAIL.COM

NOTES

(1) In this study, affordability is defined as the extent to which national health insurance schemes are able to cover the costs of the medical needs of patients within the available health budget. Individual affordability is linked to the financial burden of cost-sharing (Kanavos et al., 2011a). Affordability is therefore the relationship between the monthly drug regimen cost and GDP per capita. This indicator can be used as a reference point for cross country comparison to analyze the cost of treatment option for different Member States (Günther et al., 2014). Availability is taken to mean the medicine of choice is available to the practitioner and patient, unaffected by the government or health facilities ability to procure it.

(2) Full report forthcoming 2015.

(3) Prices of all available strengths and package sizes of the five selected active ingredients were surveyed. For subsequent comparison, only medicines with the identical strength were considered. To adjust to different package sizes, the unit price of one pill was calculated.

(4) The nominal value of a good is its value in terms of money rather than some other good, service, or bundle of goods.

(5) The prevailing model of innovation for new medicines allows the innovator company to recoup hypothetical R&D costs through high prices while being protected against competition by intellectual property rights enforcement. An innovation model based on patent monopolies therefore relies on high prices for the resulting medical technologies.

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COLOPHON

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The North-South divide in access to quality-assured medical products – A public health problem and an ethical challenge

Access to essential medicines, at affordable prices and with appropriate quality standards, is a fundamental prerequisite to ensure universal access to health. In recent years, we witnessed an impressive mobilization of the scientific community and civil society to improve financial access to newly-developed essential medicines, and the lessons learned in the field of HIV/AIDS represent a valuable model for other infectious diseases as well as non-transmissible diseases. Unfortunately, there hasn't been a comparable mobilization for overcoming the North-South divide when it comes to quality of medicines.

A SITUATION OF MULTIPLE QUALITY STANDARDS

The rapid globalization of the pharmaceutical market observed during the last three decades has not been accompanied by a globalization of pharmaceutical regulation. According to the World Health Organisation (WHO), only twenty percent of countries have fully operational national regulatory authorities (NRAs), while the capacity for medicines regulation (e.g. for thoroughly assessing products' dossiers before registration) is 'varying' in 30% of countries and 'very limited or absent' in the remaining 30%. [1] This led to a situation of multiple pharmaceutical standards. The quality of medicines largely depends on the level of income and regulation in the country of final destination, and people in many middle- and low-income countries (LMICs) are exposed to the risk of receiving poor-quality medicines. [2]

Poor Quality Medications

In general, poor-quality medicines can be lumped into two broad categories.

First, falsified medicines (or falsely-labelled, counterfeits) are products that are intentionally and fraudulently produced. They often contain no or less active ingredient than labelled, or plainly the wrong active ingredient. However, they can confusingly also contain the right active ingredient, in the right quantity, but simply infringe the trademark of a patented product. This latter example does not represent a public health threat for patients but merely an intellectual property problem. Falsified medicines are always the result of a criminal activity, carried out outside any regulatory and legal framework.

The second category consists of substandard medicines which are the result of unintentional actions, such as degradation due to faulty storage conditions or errors during the manufacturing process, which most often results in a different amount of active ingredient than labelled. This is due on the one hand to the manufacturers' lack of capacity or negligence, and on the other hand to the NRAs' lack of resources for enforcing regulatory supervision of medicines manufactured, imported and distributed in their territory.

From a public health perspective, substandard and falsified medicines are equally dangerous, [5] i.e. they may all cause direct toxicity, lack of therapeutic efficacy, and emergence of resistances.

There is widespread evidence that poor-quality medicines are prevalent in LMICs. Most data come from the field of malaria, since the steep rise in resistance to old medicines has triggered a strong awareness of the risks linked to poor-quality antimalarials, [6] which will be discussed in more detail by Thomas Dorlo on page 13-15. However, quality problems have been documented also for other medicines, such as those for treating tuberculosis, [7] infectious diseases, [8] tropical neglected diseases, [9] chronic diseases, [10] and others [11]. The *in vitro* diagnostics and medical devices are not spared by this plague, [12] and it is likely that the phenomenon remains underestimated. In fact, evidence from the literature comes either from retrospective surveys or from cases of acute toxicity, [10] while cases of sub-therapeutic efficacy (e.g. due to under-dosing of the active ingredient, poor stability or insufficient bio-availability) will often go undetected. The weakness of pharmaco-vigilance systems in many LMICs further aggravates the risk of underreporting.

THE WAY FORWARD

The WHO Pre-qualification project [13] provides a precious support for purchasers of medicines in LMICs for some specific diseases (http://apps.who.int/prequal/), but unfortunately no comprehensive mechanisms exists yet covering all essential medicines. In order to *prevent* poor quality medicines from reach-

ing patients in LMICs, and to prevent these patients from being *harmed* rather than *cured* by a therapeutic intervention, the following measures should be urgently implemented:

Re-enforcing the regulatory capacity in LMICs;

Strengthening the national and international regulation, with special focus on initiatives that promote collaboration, knowledge-sharing, resource-sharing and networking among Northern and Southern NRAs; [14]

Expanding the scope of the WHO Prequalification programme;

Educating and convincing the main public and private stakeholders to adopt and implement procurement practices for medicines and other medical products based on stringent quality assurance criteria. [2]

The enforcement of quality standards in pharmaceutical production and distribution is generally seen as a purely technical subjects. In reality, the poor enforcement of regulatory supervision on medicines' manufacturers and wholesalers exposes the patients to poor-quality medical products, which will in turn result in avoidable *harm*. Correcting the current situation of variable pharmaceutical standards is in the first place not a technical problem but an ethical imperative linked to the medical ethics' principles of beneficence and non-maleficence. [15]

RAFFAELLA RAVINETTO
CLINICAL SCIENCES DEPARTMENT, INSTITUTE TROPICAL MEDICINE ANTWERP, BELGIUM
CLINICAL PHARMACOLOGY AND PHARMACOTHERAPY, KU LEUVEN, LEUVEN, BELGIUM;
RRAVINETTO@ITG.BE

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The content of this paper is drawn from the experience of QUAMED, a programme of the Institute of Tropical Medicine of Antwerp which brings together humanitarian NGOs and non-profit procurement centres, to promote appropriate quality standards for the procurement of medicines in LMICs (https://www.quamed.org/fr/accueil.aspx).

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PHOTO: DR. MAE MELVIN - THE CENTERS FOR DISEASE CONTROL AND PREVENTION

Plasmodium malariae

Falsified and substandard antimalarials – A fatal threat to malaria control

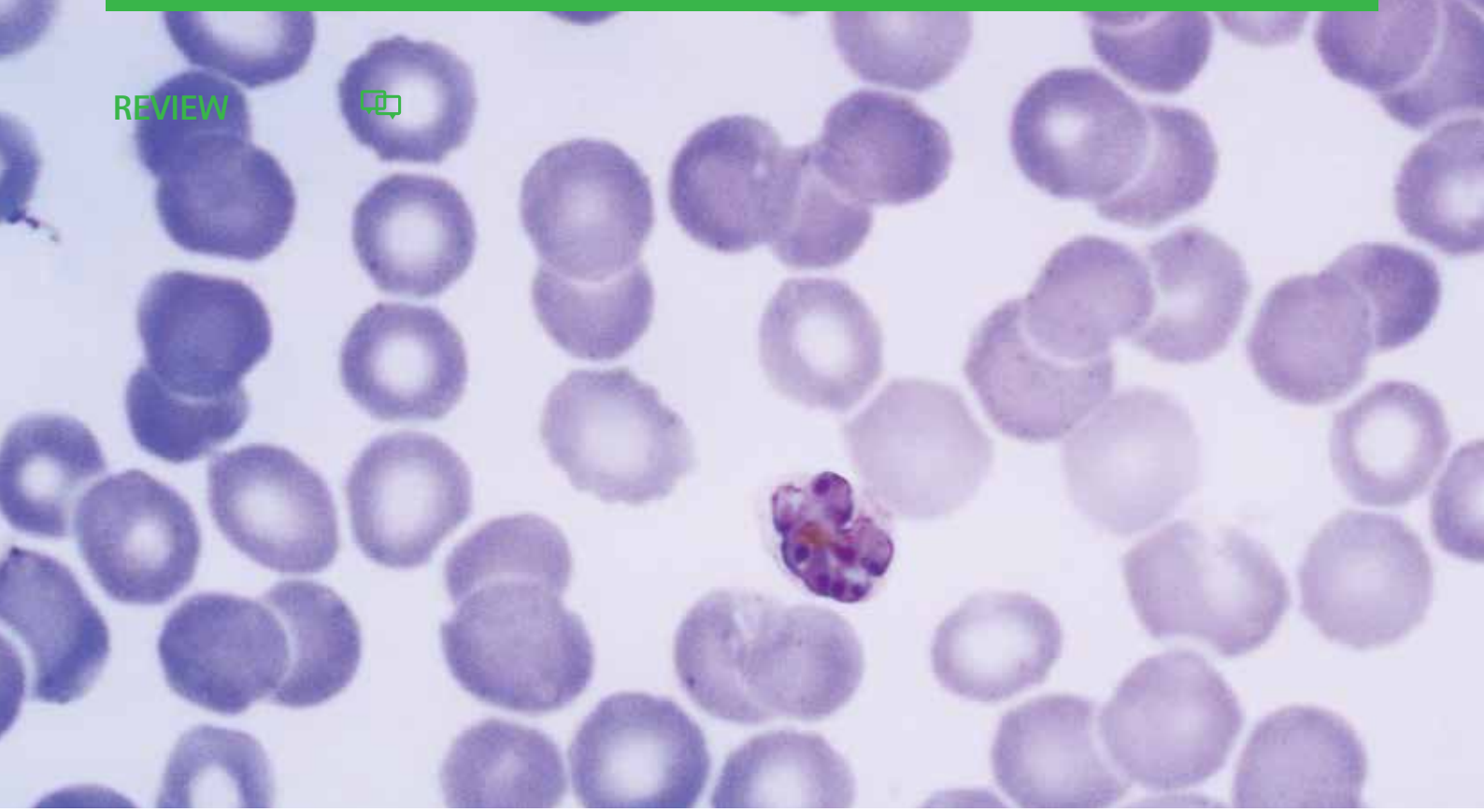
Shortly after the European introduction in the 17th century of the expensive 'fever tree bark' to treat 'intermittent fever', accounts of fake Peruvian cinchona bark without any fever-reducing activity were reported. Falsification of medicines has been haunting malaria patients ever since. The reliability of health systems, control programmes, and public health interventions stand or fall by the quality of medicines. For malaria, antimalarials with no or only a little active ingredient have not only contributed to the rapid emergence of drug resistance against traditional compounds but also to a countless number of avoidable deaths due to untreated infections. In this brief overview, I will discuss the impact of falsified and substandard medicines in the field of malaria and some of the current challenges and prospects for tackling this globalized health problem.

A GAME OF DEFINITIONS

Awareness of the general problem of poor quality medicines has certainly increased over the past years, culminating in the adoption of a so-called Member State Mechanism by the World Health Assembly in 2012 to unite international action to tackle this public health threat. Sadly, very little real action has been taken since then, mainly because there is little consensus on the definitions among stakeholders due to the differences between public health perspectives and trade perspectives. Pharmaceutical companies are mainly concerned about intellectual property protection and pricing of their products, whereas (non-)governmental organizations focus on public health implications and the universal right to health. The terminology is therefore still confused. In general, 'poor quality' medicines can be lumped into two broad categories, falsified and substandard medicines, which were discussed previously in the article by Raffaella Ravinetto (see the box on page 11). Obviously these two categories are often difficult to distinguish because they are generally based on the motive of the manufacturer, which is not only difficult to prove but is often also irrelevant from a patient perspective. The distinction between falsified and substandard medicines is nevertheless regarded as important, because they represent deficiencies in different systems that might require different solutions, which will be covered more extensively later.

DOUBLE STANDARDS

In regions where malaria is endemic, antimalarial medicines are widely available over-the-counter and often self-prescribed, with a lot of presumptive treatment of undiagnosed fevers. It is estimated that 300 to 500 million courses of antimalarial treatment are used every year worldwide. [1] The combination of poor consumer and health-worker knowledge about drugs and drug quality and the limited budget of poor patients makes antimalarial drugs a very attractive target for drug counterfeiters. Unfortunately, counterfeiting is not the only problem. The World Health Organization (WHO) estimated that only 7% of sub-Saharan African countries had a 'moderately functioning' National Regulatory Authority (NRA).



The globalized pharmaceutical market, with the mainstay of generic production taking place in South Asia, has adapted to the differences in regulatory oversight which has led to different quality standards during (lawful) medicine production. [2] Both falsified and substandard antimalarials afflict therefore mainly the poorest and most vulnerable malaria patients. Since it is difficult to differentiate falsified from substandard drugs, the prevalence numbers below often include both categories and refer to the failing or passing of chemical and packaging analyses.

EPIDEMIOLOGY OF A PANDEMIC

Even though reports of poor-quality medicines have increased particularly in the field of malaria over the past two decades, the actual extent of the problem is difficult to assess due to methodological constraints in performing drug quality surveys. Concerns about the emergence and spread of resistance against many antimalarials have boosted investigations in the field of antimalarial drug quality, but these have not always applied proper methodologies, randomization and standardized chemical assays. [3] Nevertheless, all reported numbers indicate a growing pandemic that affects not only Southeast Asia, where the first reports on falsified artesunate originated, [4] but increasingly also sub-Saharan Africa. A meta-analysis of 28 antimalarial quality surveys published between 1999 and 2011 showed that, both in South Asia (7 countries) and sub-Saharan Africa (21 countries), 35% of the tested drug samples failed the chemical analysis, with either too little or no active ingredient. [5] A larger meta-analysis, including 529 surveys since 1946, indicated that almost all types of antimalarial drugs are affected, but the majority of surveys analysed samples of artesunate, chloroquine and sulphadoxine-pyrimethamine. [1] Oral artesunate was most commonly reported as being of poor quality, with 61.9% failing chemical or package analysis, compared to 30.1% overall. Falsified or substandard artemisinin derivatives-based combination therapies have hardly been encountered in Asia, with only 1 report on a Chinese seizure of drugs intended for export to Africa, in contrast to numerous reports from Africa (with 20.4% failure rate).

Nevertheless, there have also been recent positive signals indicating that the situation is improving in some countries. In Laos, no falsified artesunate was detected in a private sector survey in 2012, while in 2003 a similar survey still revealed 84% being falsified. [6] Also recent reports from both Cambodia and Tanzania indicated positive changes compared to previous reports, with no falsified artemisinin derivatives-based antimalarials and lower prevalence rates of substandards being found in the current surveys. [7, 8]

MAPPING THE GAP

There remain many blind spots on the antimalarial quality map. For approximately 60% of the 104 countries where malaria is endemic, we have no information at all on the prevalence of poor quality antimalarials. In particular, the situation in South and Central America remains unknown, with antimalarial quality data only available from 19% of the region's malarious countries. Also, large parts of Central Africa have been neglected. There is only a single antimalarial quality survey reported from the Democratic Republic of Congo, Angola and Gabon, while these countries represent 40% of the estimated global malaria burden. So there are major concerns related to underreporting in almost all malarious regions. In addition, the origin of both falsified and substandard antimalarials is difficult to establish, due to a lack of regulatory oversight and forensic investigations in this area. One important tool has proven to be forensic pollen analysis, by which

tiny traces of plant pollen that ended up in the drug samples during the manufacturing process can identify areas where these plants are common. This has consistently shown that the criminal production of falsified antimalarials mainly takes place in East Asia, even for the falsified drugs detected in Africa. [9]

IMPACT

Obviously, poor quality antimalarials containing little or no active ingredient lead directly to increased morbidity and mortality due to prolonged sickness and unresolved infections. Estimates indicate that, in 2013, ineffective poor quality antimalarials alone caused 122,350 deaths in children under the age of five in sub-Saharan Africa. [10] But falsified antimalarials are often not just inert but often contain other active and potentially harmful, ingredients. In the various antimalarial quality surveys, up to 20 different active ingredients have been found in falsified antimalarials, ranging from (a low amount of) other antimalarials to diazepam, chloramphenicol and even sildenafil, [1] which all may cause confusing adverse effects in unsuspicious patients. Patients may lose confidence in health-care providers and pharmacies and in the case of falsified medicines also in pharmaceutical brands. It leads to a financial loss for patients and their families but also for governments and complete health systems. However, the biggest threat resulting from poor quality antimalarials is their contribution to the emergence of drug resistance. The wide-spread availability of poor quality artemisinin-based drugs containing subtherapeutic amounts of active ingredient have arguably contributed to the tragic emergence of artemisinin-resistance in P. falciparum on the Thailand-Cambodia border. [11] For combination therapies, the risk of engendering drug resistance is dual: both the subtherapeutic active ingredient as well as the 'unprotected' co-ingredient increase the risk of resistance. Poor quality artemisinin derivatives-based combination therapies have been found all over the African continent. [1] These combination therapies are among the most crucial tools to control malaria in Africa. Losing them to drug resistance would be a public health catastrophe.

CONTROL MEASURES AND CHALLENGES

There is no simple and fast solution to ensure good quality of all available antimalarials. Many proposed control measures focus on the detection of poor quality antimalarials, e.g. by standardized analytical methods, and on promoting prosecution of illicit counterfeiters. However, many of these approaches focus solely on falsified medicines and intellectual property protection. Substandard production by genuine manufacturers remains poorly addressed, partly because there is no consensus on its definition. Public health should nevertheless always be the prime consideration in combatting poor quality medicines. [12] Around 30% of countries have a non-functional or even non-existing NRA. Financial and technical support of regional and national regulatory authorities and the development of regional analytical laboratories in malarious regions are therefore absolutely pivotal to enable any interventions, surveys and routine inspections. This would not only allow more reliable screening for falsified medicines but also prevention of substandard production in lawful manufacturing facilities by increased enforcement of quality standards on manufactures and distributors. The investment and efforts in access campaigns to make essential antimalarials available can only be effective if their quality is ensured. Without prioritizing access to good quality antimalarials, current efforts to control malaria in Africa and Southeast Asia may be futile.

THOMAS P.C. DORLO, PHD
RESEARCHER/LECTURER DEPT. PHARMACEUTICAL BIOSCIENCES, UPPSALA UNIVERSITY, UPPSALA, SWEDEN
DIV. PHARMACOEPIDEMIOLOGY & CLINICAL PHARMACOLOGY, UTRECHT INSTITUTE FOR PHARMACEUTICAL SCIENCE, UTRECHT UNIVERSITY, UTRECHT, THE NETHERLANDS
T.P.C.DORLO@UU.NL

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Improving insulin availability and affordability

Insulin is an interesting medicine. It was discovered over 90 years ago yet the life expectancy today for a child with Type 1 diabetes in Sub-Saharan Africa is as low as one year. [1] About 100 million people worldwide need insulin to manage their diabetes. However, more than half of these people cannot afford and/or access this essential medicine. This was illustrated in a 2013 survey in Burundi undertaken using the World Health Organisation (WHO)/HAI medicine price and availability methodology. [2] In public sector facilities, the mean availability of regular human insulin 100IU/ml was only 17.4%. When available, the lowest paid unskilled government worker would have to work about 6 days to pay for one 10 ml vial (excluding other costs such as syringes, blood glucose monitoring, consultation etc.). Accessing this insulin in other sectors would be even more challenging, as availability was only 7% in private pharmacies and 0% in mission facilities.

This situation is not specific to Burundi. Poor insulin availability and/or unaffordable prices are found in other low- and middle-income countries. The problem also exists for other non-communicable disease (NCD) medicines, which led the WHO to set a voluntary target of 80% availability of affordable medicines, including generics, to treat major NCDs in the public and private sectors of countries by 2025. Much needs to be done, at the global and national levels, for this target to be met for insulin.

To address inequities and inefficiencies in the global insulin market, the barriers to accessing insulin must be identified. Unlike many other medicines for NCDs, the global insulin market is dominated by only three manufacturers (99% by value and 96% by volume), namely Novo Nordisk, Eli Lilly and Sanofi-Aventis. Is this lack of competition a factor? Are mark-ups, taxes, tariffs and other 'add-on' charges in the supply chain resulting in high insulin prices for patients? Is it that insulins are not included in national Essential Medicines Lists so they are not procured by governments? Is need not being accurately assessed? Is it that governments are buying higher-priced analogue insulins instead of human insulin?

These and other issues regarding the global insulin market are currently being studied by HAI, David Beran (Geneva University Hospitals and University of Geneva) and Richard Laing (Boston University School of Public Health) in a project entitled 'Addressing the Challenge and Constraints of Insulin Sources and Supply (ACCISS) Study.' The project includes a large group of leading international experts as members of its Advisory Group plus a Technical and Advocacy Group. It is funded by a grant from The Leona M. and Harry B. Helmsley Charitable Trust.

The objectives of the ACCISS Study are to:

- develop and provide a comprehensive, first-of-its-kind evidence base on the global insulin market, including the type, extent and impact of barriers to global insulin access;
- develop innovative models of supply and interventions, in collaboration with multiple stakeholders, to overcome the barriers to global insulin access, learning from other pioneering access programs;
- develop an advocacy network, along with a toolbox of advocacy materials, in collaboration with multiple stakeholders, to reduce or eliminate the barriers to global insulin access.

The three-year study, which was launched in January 2015, is being conducted in three phases:

Phase 1: Mapping the insulin market from different angles
Researchers will map the global insulin market to determine which pharmaceutical companies manufacture and distribute insulin, formulations, prices, trade issues, tariffs, market issues, and regulatory issues related to market authorisations for biosimilars. Current initiatives to improve access to insulin developed by the industry and the International Diabetes Federation (IDF) will also be examined.

Phase 2: Understanding who produces insulin and challenges in the distribution channel
Researchers will visit insulin biosimilar manufacturers identified in phase 1 to assess their market reach, quality assurance standards and the types of insulin that they produce. Manufacturers that may be capable of producing large-scale, quality-assured insulin will be identified. The distribution chain will also be assessed to measure add-on costs in the supply chain to assess their impact on the final patient price.

Phase 3: Developing interventions to improve access to insulin

The main activity in Phase 3 will be a multi-stakeholder meeting bringing together a variety of stakeholders to present the results from the ACCISS Study and develop interventions to improve global access to insulin. It is hoped that piloting these interventions nationally will be undertaken in subsequent phases of the project.

It is an ambitious project that will hopefully shed greater understanding on the barriers to accessing insulin and offer countries options to meet the WHO target and, most importantly, improve the health and longevity of people who need this important medicine.

MARGARET EWEN
HEALTH ACTION INTERNATIONAL (HAI)
MARG@HAIWEB.ORG

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ANNUAL CONGRESS ESSENTIAL MEDICINES

The use of sub-dermal contraceptive implants in South Africa

In Mpumalanga Province, South Africa, teenage pregnancy rates as well as unintended pregnancies are extremely high. [1] Family planning services are available but basic, proper explanation and informed consent is unavailable, and several other barriers to good family planning services exist. Six out of 28 hospitals offer termination-of-pregnancy services. Because of a largely unmet need for family planning and access to safe abortion services, many women decide to go to backstreet 'doctors' performing illegal abortions. [2]

Long-acting hormonal sub-dermal implants have proven very effective in reducing teenage and unwanted pregnancies. [3] In June 2014, South Africa rolled out a programme to freely provide this type of contraceptive for all women of childbearing age. Professional nurses and midwives from clinics and hospitals were trained on insertion of the implants. Subsequently, clinics and hospitals were stocked with the product, after which things moved quickly. The response among women was positive, and within the next six months over 6000 women in Mpumalanga received the implant. Many unintended pregnancies were prevented, and dangers related to abortions and ectopic pregnancies were averted in all these women. It seemed the need for family planning was finally going to be met. Unfortunately, it turned out that the demand was higher than the supply.

CHALLENGES

In order to meet the demand, the initially trained nurses were encouraged to transfer their skills within the healthcare facility. They trained their colleagues, who in turn trained student nurses. Within a short time, these student nurses were placing most of the implants, and along the way many skills got lost in translation.

With a loss of the necessary training and skills, the placement of the implants was not always done correctly. Due to incorrect placement, several cases of implant migration were reported and in some instances even into the circulatory system and distant organs.

The second challenge was the interaction with cytochrome P450 3A4 (CYP3A4) inducing drugs. [4] With an HIV prevalence of about 36% amongst women attending antenatal clinics [5], many women in Mpumalanga are on antiretroviral drugs or tuberculosis (TB) treatment. Interaction of levonorgestrel with these drugs could lead to decreased bioavailability of the hormone, increasing the risk of pregnancy. Healthcare workers were advised to refrain from insertion of the implant in any patient with HIV or TB. One could argue that it might be a better option to let the patient make an informed decision while advising the concurrent use of barrier contraceptive methods.

But the third and probably most important challenge was the lack of proper counselling before insertion of the implant. Good counselling is essential for each woman to make an informed choice on her contraceptive use. In a population with already high levels of discontinuation of contraception, many women will resort to abortions. [5] Although healthcare workers were trained in providing counselling to women, in practice counselling was inadequately done. The biggest resulting problem was the lack of an explanation of the possible effects of the device on menstruation. It is known that the implant can lead to altered or absent menstrual periods. If these and other (especially transient) side effects are not communicated properly, women will have false expectations, and many will not be satisfied with the implant. One should also consider the importance of cultural beliefs in this regard. In some cultures. the lack of menstrual periods is unacceptable.

Within six months after insertion of the implant, many women came back with the request to have the implant removed. The reasons mentioned were mainly related to cultural beliefs. Women were 'feeling hot', had a 'feeling the blood was accumulating in the body', 'veins were becoming swollen' and they had 'abdominal pains because the blood did not come out'. Other side effects mentioned were heavy bleeding, libido changes and headache. No woman mentioned the wish to become pregnant as the reason for request of removal. Attempts by healthcare workers to convince the patient of the safety of the implant were at this stage unsuccessful, as counselling should have been done before insertion. Because nurses at the clinics lacked the resources to remove the implants, they had to refer these patients to a hospital, further increasing the workload for doctors and hospital nurses.

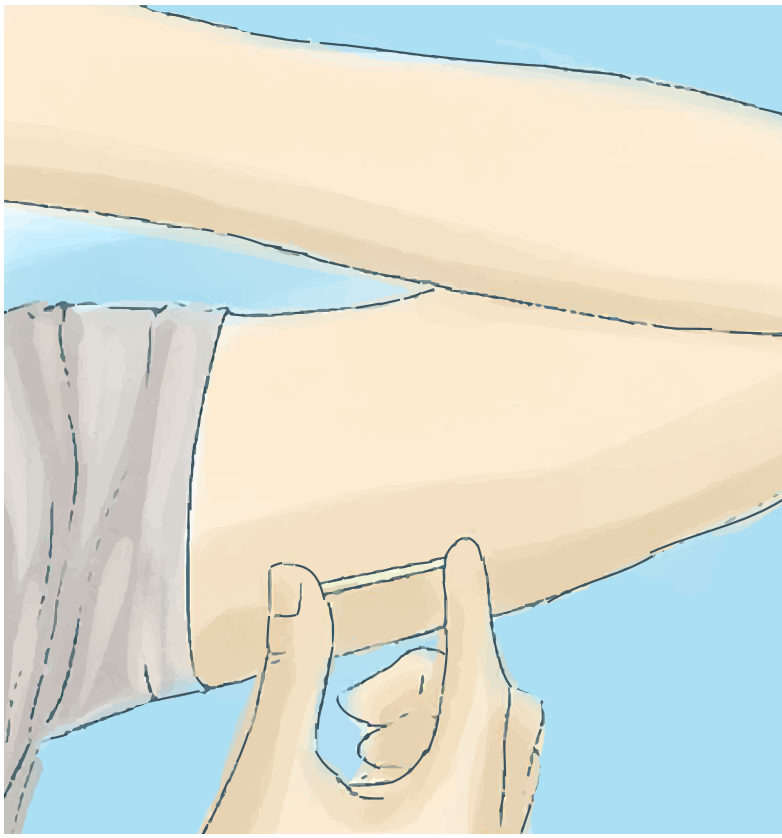
CONCLUSION

Due to these challenges, the insertion of the implant was suspended in Mpumalanga province, six months after initiation. A survey was performed with the goal of improving the programme. But even if the programme is improved and restarted,

challenges will remain, as suspension of a programme can be bad for its image.

When healthcare professionals are trained to provide this service, their skills should be regarded as exclusive and not transferable within the facility, e.g. by awarding a diploma and empowering patients to ask for this proof of training. With increased demand, the number of procedures that can be done in a certain time frame will be less, but quality should be more important than quantity. More focus should be placed on counselling, especially with regards to cultural beliefs. An outreach campaign solely for counselling, and without direct insertion, leaving the women with sufficient information and time to make an informed choice on their contraceptive use, should be considered. Interactions with other drugs should be properly investigated and communicated before a programme is rolled out. And finally, healthcare workers trained to insert an implant should also be trained and provided with resources for removal.

Nevertheless, it is impressive that an effective long-term contraceptive can become available free-of-charge for so many women with a need for family planning. In learning from these challenges, we can only hope that many more women in South Africa will be able to have access to long-term family planning services and to make an informed choice. We will then be able to further decrease the numbers of unwanted pregnancies and induced abortions, thereby saving the lives of many women and improving the lives of families and children.



Birth control implant. A small rod is inserted in the arm, and it releases hormones to prevent pregnancy for up to three years. It must be inserted and removed by a health care provider.
Source: WIKIHOW

ME ZELDENRUST
TROPICAL DOCTOR, TONGA HOSPITAL, MPUMALANGA, SOUTH AFRICA

G. GOOSEN
DISTRICT SPECIALIST OBSTETRICS AND GYNAECOLOGY, EHLANZENI DISTRICT, MPUMALANGA, SOUTH AFRICA

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Balancing access and excess: tackling the complexity of Antibiotic Resistance

The emergence and spread of bacteria resistant to existing antibiotics is of growing global concern. Recent national and international actions have raised the political profile of Antimicrobial Resistance (AMR), such as; the adoption of the World Health Organization's (WHO) Global Action Plan on AMR in May 2015, the White House Forum on Antibiotic Stewardship and the G7's communiqué in June 2015, and the ongoing O'Neill Review on AMR in the United Kingdom. High rates of AMR have been noted in all regions of the globe. [1] At a minimum, the gradual loss of effective antibiotics will undermine our ability to fight infectious diseases. According to the O'Neill Review on AMR, up to 10 million people per year could die by 2050 due to resistance, compared to an estimated 700,000 deaths annually at present. [2] Furthermore, this figure does not capture the indirect impacts of AMR beyond the risk to mortality, such as the effects on animal health, food security and environmental risks. Antibiotic resistant bacteria spread through the environment and from individuals to populations and across countries as people and animals move around; the complexity of this issue is impacted by the broad and multi-sector drivers that are believed to be exacerbating resistance across the human, animal and agricultural/environmental sectors. It is universally recognized that an effective response needs to simultaneously address both the development of new therapies and measures to slow the emergence of resistance. To be truly effective, these efforts have to recognize the considerable differences in the risks and challenges faced by governments and populations across the world. Low and Middle Income Countries (LMICs), where the majority of the world's population live, not only pose a particular challenge in addressing antibiotic resistance but also will face a disproportionate burden. [3] It is in these countries that the issue of access and excess reveals the complexity of tackling AMR.

ACCESS AND EXCESS: A PARTICULAR CHALLENGE FOR LMICS

Access to antibiotics is a major concern in many LMICs, as seen with the high cost of the most recent and efficacious antibiotics or the unaffordability of appropriate doses and the increasing availability of counterfeit and low-quality antibiotics. [4] A common feature of health services in LMICs is the emergence of mixed or pluralistic health systems, where households use a vast range of public and private health care providers, many of whom are not controlled by national health authorities. These providers span a spectrum from medical specialists to informal providers, often combining both Western and local medical systems. There is evidence that these markets have widened the access to antibiotics and enabled people to treat many infections and reduce mortality. However, they also encourage excess use of antibiotics (self-medication, non-compliance, inappropriate use) and behaviour likely to encourage the emergence of resistance. [5]

The ways antibiotics are used are deeply embedded in meanings, networks, markets and norms. Some pervasive beliefs and meanings have been attached to antibiotics which influence how they are used. [6] Several factors influence deviations from what would be considered best practice for both providers and users, such as financial incentives, poverty, conflicting advice, peer influences, advertising pressures, perceived demands of patients, lack of education, inaccessibility to health care and diagnostic facilities, and ineffective law enforcement. [7]

One suggestion for addressing the challenge of antibiotic resistance would be to enact and enforce laws that restrict the right to prescribe antibiotics to licensed health workers. In the short-term, this may not be realistic in many pluralistic health systems, where people seek treatment from more informal providers as their only available access to medicines. This presents a hard choice to governments: denying many people access to life-saving drugs or turning a blind eye to nominally illegal practices which can exacerbate resistance. The alternative is to find ways to engage with these markets to improve antibiotic use. Tackling the access versus excess issue requires deeper understanding of the factors that influence providers and users and developing the role of government as regulator and steward of the health sector. [8]

A COMPLEX ADAPTIVE SYSTEM

Ensuring universal appropriate access to antimicrobials is not only a critical part of realizing the right to health, it is necessary for mobilizing effective collective action against the development and spread of AMR. The issue to tackle is understanding how the flow of antibiotics should be controlled in a system. When patients need drug therapy, how do we ensure that the appropriate, effective, safe drug is prescribed for them, that it is available at the right time at a price they can afford, that it is dispensed correctly, and that it is taken in the right dose and for the right length of time. [9] This issue clearly involves a complex system of interacting components such as behaviours, financing, regulation and effective monitoring, whilst simultaneously involving a number of actors, organizational levels and possible outcomes. [10] Strategies to ensure access to and rational use of antibiotics will need to be designed with this complexity in mind.

There are indeed many strategic points of intervention; a realignment of incentives to providers, prescribers, dispensers, and users is important to encourage correct use of antimicrobial treatment. However, In order to be effective, these strategies must be sustainable, focus on reorientation of social norms, multidisciplinary, and multitier (pharmaceuticals, food and agriculture, human resources, financing, and information systems), linking science to practicality. These measures need to be informed by proven interventions built on effective surveillance systems. Although regulation is crucial to safeguard access to antibiotics, a transition towards such regulation needs governmental commitment and improvements in health systems that are not possible in many countries. Hence, antibiotic stewardship programs need to be adjusted to local conditions.

THE WIDER CONTEXT

In LMICs, the spread of resistant bacteria is facilitated by poor hygiene, contaminated food, polluted water, overcrowding, direct cross-species transmission from animals, and increased susceptibility to infection because of malnutrition or chronic illness and/or infections causing immunosuppression such as HIV. Strategies to tackle access and excess also need to focus on these deeper facilitators of resistance. Similarly, the number of possible interventions may appear to be straightforward, but in fact they influence complex human, animal and environmental landscapes, especially when used in combination, and can result in many other effects, variable in different places and sometimes unwanted. Being cognizant of this wider context is paramount to creating a sustainable outcome, hence the calls to view resistance through the lens of a holistic, ecological, unified approach to health. [11]

THE WIDER COMMITMENT

Bridging the divide between individual and collective action is key when it comes to tackling AMR. The implementation of a sustained effort to achieve system-wide changes in the use of current and future antibiotics requires informed and committed collaboration at both national and global levels. In May 2015, the WHO released a Global Action Plan on antibiotic resistance, but it remains to be seen whether effective global governance institutions can be created. The need for political commitments, frameworks and institutions at the national level is also recognized.[12] Countries that have implemented comprehensive national strategies and contextualized, targeted and prioritized approaches have been the most successful in controlling resistance. [13] However, these programs need time and patience to be set up and need to be backed by visionary governments with adequate funding. In resource-poor countries, there has been much less progress. The bottlenecks for implementing programs are largely a result of insufficient leadership, commitment, and funding. [14] Involving the key players, such as global health donors, pharmaceutical companies, technical agencies, NGOs, governments, patients, and physicians, in partnership arrangements while protecting the interests of the relatively poor and powerless will be key to creating sustainable approaches to tackle AMR.

OUTLOOK

To ensure that a global strategy will effectively address AMR, measures need to tackle the appropriate use of antibiotics whilst ensuring just and sustainable access to antibiotics in LMICs. Finding the right balance between access and excess will require knowledge of the wider complex system of interacting components including behaviour, financing, and regulation and monitoring at the various organizational levels and in the human, animal and environmental landscapes involved. Solutions need to focus on multifaceted and multilevel interventions supported by active participation of a variety of actors that define local barriers and beliefs, which can vary widely between cultures, countries, and regions. A single approach is unlikely to suit all settings; sustainable change will require mutually reinforcing strategies at local, national and global levels.

DR GEMMA L BUCKLAND MERRETT
RESEARCH FELLOW IN GLOBAL HEALTH POLICY; CENTRE FOR GLOBAL HEALTH POLICY, UNIVERSITY OF SUSSEX, UK
G.BUCKLAND-MERRETT@SUSSEX.AC.UK

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Spontaneous hyphema of the right eye

Figure 1

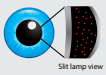
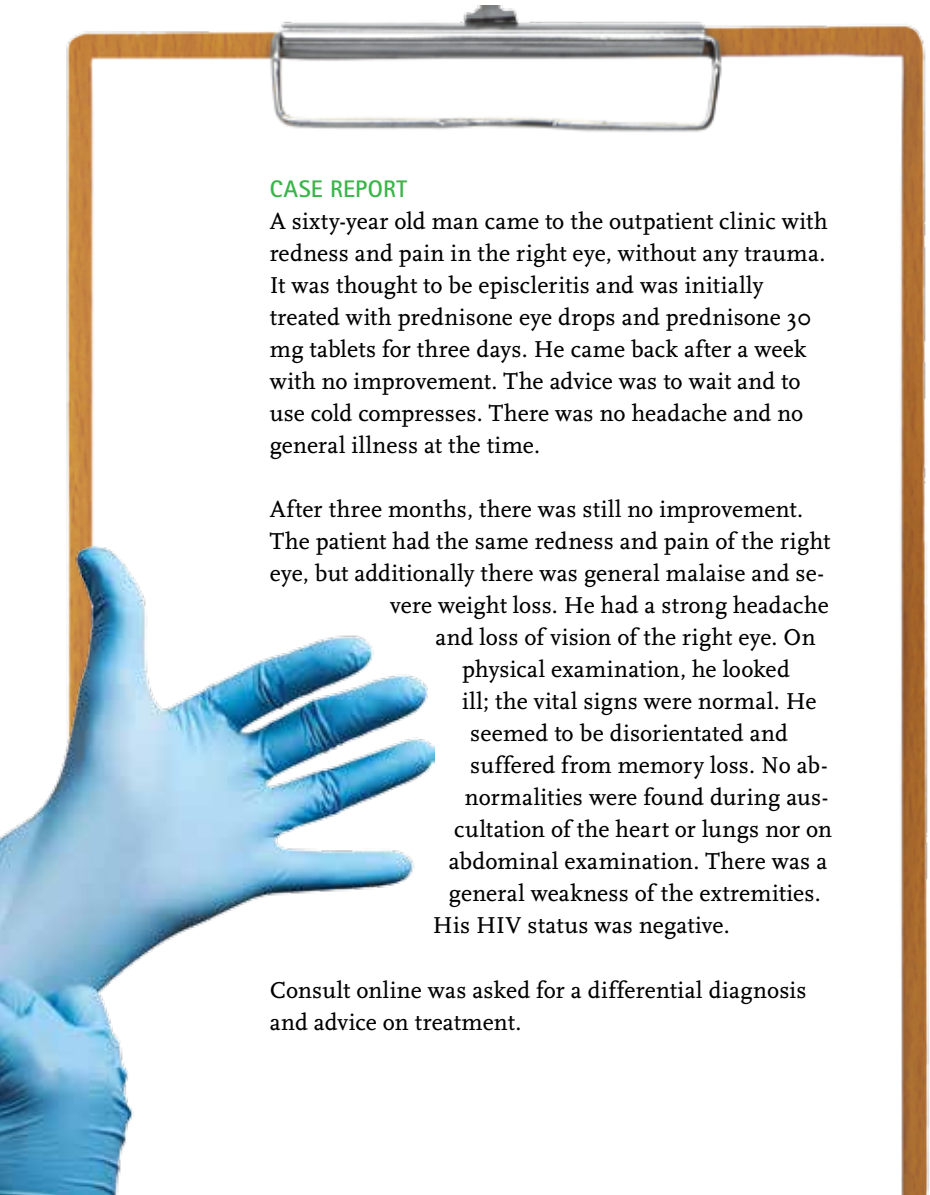
Grade	Anterior chamber filling	Diagram	Best prognosis for 20/50 vision or better
Microhyphema	Circulating red blood cells by slit lamp exam only		90 percent
I	<33 percent		90 percent
II	33-50 percent		70 percent
III	>50 percent		50 percent
IV	100 percent		50 percent

Figure 2 . Hyphema grading table (Brandt et al.)[1]



CASE REPORT

A sixty-year old man came to the outpatient clinic with redness and pain in the right eye, without any trauma. It was thought to be episcleritis and was initially treated with prednisone eye drops and prednisone 30 mg tablets for three days. He came back after a week with no improvement. The advice was to wait and to use cold compresses. There was no headache and no general illness at the time.

After three months, there was still no improvement. The patient had the same redness and pain of the right eye, but additionally there was general malaise and severe weight loss. He had a strong headache and loss of vision of the right eye. On physical examination, he looked ill; the vital signs were normal. He seemed to be disorientated and suffered from memory loss. No abnormalities were found during auscultation of the heart or lungs nor on abdominal examination. There was a general weakness of the extremities. His HIV status was negative.

Consult online was asked for a differential diagnosis and advice on treatment.

SETTING

Kikori rural hospital is a district hospital in Papua New Guinea. It is located in the jungle and it can only be reached by boat or plane from Port Morseby. The nearest referral hospital can be reached after two days of travel. In case of emergency, a helicopter of the nearby oil company can be used, provided that the weather conditions are good. Annually, this hospital provides healthcare to 30,000 patients and has a capacity of 80 clinical beds. There are two doctors working in the hospital, and there is one operating room. At the time of presentation of this patient, there was a tuberculosis epidemic in this area.

ADVICE FROM THE SPECIALISTS

Two of the specialists responded within a day. They said that the photo (Figure 1) was suggestive for hyphema, blood in the anterior chamber of the eye. Presumably, the intraocular pressure was raised, and this can cause headache, nausea and general malaise. However, the cornea looked clear. This argued against a highly raised intraocular pressure, as the cornea would then show a greyish glow and there was no evidence for hematocornea, a discoloration of the cornea. To test if the eye pressure is raised, the cornea can be palpated while the patient is looking down. The resistance must be compared to the other normal eye.

If the intra-ocular pressure is raised, the pressure can be released by making a small incision in the anterior chamber of the eye, after retrobulbar anaesthesia. Then the blood can be rinsed out of the anterior chamber with a cannula. If this does not lower the eye pressure and the eye stays painful and blind, there are a few options such as atropine eye drops and prednisone eye drops. If there is no vision left at all, a retrobulbar injection with alcohol 70% can be given after an injection with lidocaine. If this is still not adequate, enucleation may be considered.

The underlying cause of the hyphema was still not clear, as hyphema alone does not cause a general illness. Presumably, it was caused by a rubeosis iridis (neovascularization of the iris), after a vascular occlusion of the eye. In most cases, there is a longstanding hypertension, but an infection or a tumour is also a possibility. Tuberculosis and syphilis can cause vascular complications and could be the underlying cause of the hyphema. It was suggested to test for TB and syphilis and to start treatment if the results were positive.

TREATMENT AND FOLLOW-UP

The patient was admitted to the hospital. Because of his poor condition and the unknown cause, he was treated with intravenous broad-spectrum antibiotics, TB medication, prednisone, and corticosteroid eye drops.

At first, his general condition seemed to improve, but the eye stayed painful and red. Unfortunately, after a few weeks, there was a deterioration and he eventually passed away. The cause of death remains unknown; there was no fever, hypertension or neurological symptoms at the time of death.

DISCUSSION

Spontaneous hyphema is an uncommon condition with debilitating consequences. The classification system for hyphema defines grade I-V (Figure 2), and this patient had a grade II-III hyphema.

Hyphema can occur spontaneously or after minor trauma in patients with bleeding tendency or conditions that cause neovascularization (rubeosis iridis) or vascular anomalies of the anterior chamber structures. [1, 2, 5] This includes diabetes mellitus, iris melanoma, clotting disorders (e.g. thrombocytopenia, haemophilia, von Willebrand's disease), and the use of antiplatelet drugs. [2, 3, 4] Infections that may cause vascular complications can also cause hyphema, such as tuberculosis, HIV and syphilis. Furthermore, several malignancies (or metastases) can also cause vascular abnormalities. [4]

The prognosis for hyphema depends on the grade (Figure 2), and the treatment of the underlying cause. Moreover, some patients are at higher risk of permanent complications and vision loss, such as patients with sickle cell disease or sickle cell trait. [2] Patients with clotting disorders or on anticoagulants are also at increased risk of vision loss because of the greater frequency of rebleeding. If possible, the clotting disorder must be treated immediately, and the patient should stop taking anticoagulants. [2, 3]

In this case, the underlying cause was not found, which can be difficult in a rural setting. One must keep in mind the broad differential diagnosis of the underlying diseases and start, as in this case, a broad systemic treatment if there are not enough resources to confirm a diagnosis.

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HANNA MATHÉRON, MD
IN TRAINING FOR DOCTOR IN INTERNATIONAL HEALTH AND TROPICAL MEDICINE
CONSULTONLINE@TROPENOPLEIDING.NL

IRIS DE RIDDER, MD
TROPICAL DOCTOR AT KIKORI HOSPITAL, PAPUA NEW GUINEA

OLEG / SHUTTERSTOCK.COM

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Netherlands Society for Tropical Medicine and International Health
President: A.A.L.J. (Ankie) van den Broek
Secretary: M.G.P. (Marieke) Lagro
Secretariat: J.C. (José) Hoppenbrouwer
P.O. Box 82
3738 ZM Maartensdijk
The Netherlands
+31(0)6-53515773
info@nvtg.org
www.nvtg.org

Werkgroep COTG (Concilium Opleiding Tropische Gezondheidszorg)
en CIGT (Concilium Internationale Gezondheidszorg en Tropengeneeskunde)
cotg@nvtg.org / cigt@nvtg.org

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