

## Developing countries take a creative approach to R&D

A few low- to middle-income countries have developed new drugs to address their public health needs while other developing countries have found innovative ways to be more active in the global multibillion dollar R&D pharmaceuticals business which is concentrated in industrialized countries.

In the late 1970s, a small Croatian pharmaceuticals company called Pliva developed an original antibiotic called azythromycin. In early trials, it proved to be effective and able to stay longer in the body tissue of animals than similar antibiotics.

At the time, the company lacked the capital to market and distribute the product worldwide. In 1981, Pliva patented the product globally and this led to a licensing agreement under which Pfizer Inc. of the United States bought the rights to sell azythromycin worldwide while Pliva continued to sell it in Central and Eastern Europe.

Today Zithromax — Pfizer's version of azythromycin — is one of the biggest selling branded antibiotics in the United States.

Producing a blockbuster drug — with more than US\$ 1 billion annual sales — came true for Croatia but remains a distant dream for most middle- and low-income countries.

It's not easy with limited funds, weak infrastructure and little or no hi-tech equipment and even when researchers in developing countries find a promising product, regulatory bodies often lack the staff and expertise needed to ensure that clinical trials are ethical and new drugs are safe.

Yet despite the challenges some developing countries including Brazil, India, Indonesia and South Africa have over the last decades built up expertise in producing generic copies of R&D products to address public health needs.

Spurred by national pride and potential economic rewards a few, notably Croatia, Cuba and India, have produced original R&D medicines too.

Of some US\$ 105.9 billion annually spent on global health research, only a fraction — 4% — or a rounded-off US\$ 4.3 billion, is spent by middle- and low-income countries, according to the Global Forum for Health Research.

Most of that — 2.4% or US\$ 2.5 billion — is public sector-funded. The remaining amount rounded off to US\$ 1.8 billion is private sector funding. The Global Forum said this includes: US\$ 1.35

billion from foreign and domestic pharmaceuticals, US\$ 80 million from domestic private funds and US\$ 300 million from the private non-profit sector.

Some public health experts question whether the US\$ 4.3 billion would not be better spent on good-value drug procurement deals.

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Indeed, many developing countries still find it cheaper to import rather than to produce drugs. But since patented R&D products are prohibitively expensive for some, smaller developing countries are importing drugs from regional economic powers: such as Brazil, India and South Africa.

Cuba is one of the few developing countries to be successful in biotech research. The Centre for Genetic Engineering and Biotechnology in Havana has produced several recombinant molecules such as interferons (proteins to fight viral infections), a hepatitis B vaccine, streptokinase (an agent used in medicines for heart disease), epidermal growth factor (a protein used in cancer medicines), and other products.

These help address public health needs in Cuba and attract revenues with exports to more than 50 countries.

The Republic of Korea's R&D in pharmaceuticals has also played a role in the country's spectacular rise from a low-income developing country in the 1950s to a major economic power.



Researchers in Brazil developing antimalarial medicines.

WHO/M. Edwards

South Africa, where about 10% of the population is HIV positive, is developing a promising vaccine tailored to its specific health needs. Most HIV vaccines being developed are for virus subtype B, the dominant strain in the United States and Europe, but there is no certainty these would be effective against subtype C of the AIDS virus which accounts for more than 90% of HIV infections in southern Africa.

The project has state and private sector funding and aims to produce a vaccine for subtype C. It was initiated by South Africa's Medical Research Council. Phase I trials started in 2003.

India's generic drugs industry has pioneered fixed-dose combination antiretroviral medicines. These are not only more affordable for poor countries with high HIV infection rates, but these two- or three-in-one pills and blister packs make it easier for patients to follow treatment.

By copying and combining two or three drugs, each originally developed by a different R&D company, Indian companies Cipla and Ranbaxy have come up with competitive products unmatched by R&D originators like multinational, GlaxoSmithKline.

That success underscores one of the greatest challenges to drug production in developing countries: ensuring that medicines meet international criteria for quality, safety and efficacy.

A report to the World Health Assembly in May 2004, called on WHO's 192 Member States to cooperate more closely on drug regulation to address the need for more stringent regulation in developing countries.

This is particularly pressing in India which will be more reliant on R&D drug innovation from January 2005, when it joins the international patent system and can no longer copy new patented drugs.

Dr C.M. Gupta, Director of the Central Drug Research Institute in Lucknow, said small pharmaceutical firms may be unable to stay afloat without government aid after India joins the international patent system.

He was optimistic about the sector's prospects as a whole, citing advantages such as lower researchers' salaries and manufacturing costs.

Gupta said his research team was devoted to finding drugs for neglected diseases and had already produced two successful antimalarial drugs.

"One advantage is that we have a large patient pool for clinical trials. Also, from discovery to pharmaceutical toxicology and clinical trials things go fast," Gupta said.

In India, researchers are looking to Ayurveda traditional medicine to find plants or herbal remedies that can be converted into modern medicines.

In South Africa, researchers are investigating a diverse plant life for new active ingredients which includes Fynbos, one of the world's six floral kingdoms that is unique to the country.

Dr William Pick, President of the Medical Research Council of South Africa told the *Bulletin* that researchers were working with 20 promising compounds or molecules derived from indigenous plants to find medicines to treat malaria and tuberculosis. Pick acknowledged the difficulties: "We lack laboratory facilities and hi-tech equipment and financing of projects is difficult."

In China, the *Artemisia annua* plant was used for centuries in traditional medicine to combat fever. Today its derivatives, usually combined with synthetic compounds, are active ingredients in several antimalarial drugs.

Rather than trying to produce the medicines itself, China has become a major exporter of artemisinin to industrialized countries, but this could change in view of the trend of outsourcing.

China has recently started to make its highly educated scientists available to companies looking to outsource some of their R&D activities for a fraction of the cost of their counterparts in industrialized countries.

Swiss pharmaceuticals giant Novartis recently formed a partnership with the government-run Shanghai Institute for Materia Medica, where scientists are trying to identify compounds derived

from traditional Chinese medicines for new medicines. Roche Ltd, also of Switzerland recently opened an R&D centre near Shanghai employing 40 Chinese scientific researchers.

Developing countries also overcome funding shortages and lack of technology by entering private-public partnerships (PPP) to develop drugs for neglected diseases.

Big pharmaceuticals companies contribute molecules, manpower and machines to non-profit groups which coordinate product development and are backed by private foundations or governments of developing countries.

There are 23 PPPs working on drugs, 16 on vaccines and 20 on non-pharmaceutical products, such as antimalarial nets. Two of those, Medicines for Malaria Venture and the International AIDS Vaccine Initiative, have several products in clinical trials.

Pharmaceutical foundations have also opened research centres for neglected diseases in developing countries: for example, Novartis in Singapore for tuberculosis and dengue and GlaxoSmithKline in Spain for developing medicines for diseases that affect those countries, such as malaria and tuberculosis. ■

Fiona Fleck, *Geneva*

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## Health worker shortage could derail development goals

Senior government and development officials gathered in the Nigerian capital Abuja agreed urgent action was needed to tackle a growing shortage of doctors, nurses and other health workers.

They warned this could undermine global efforts to cut poverty and disease.

The High-Level Forum meeting on the health Millennium Development Goals, on 2–3 December, focused on strengthening health systems and ways to increase the volume, coordination and efficacy of aid to achieve the goals. Officials agreed that solving the crisis in human resources was key to advancing their development agenda.

"When aid is unpredictable, we cannot blame planners in our countries for being overcautious," said Nigerian Health Minister Eytayo Lambo. "We simply cannot commit to hiring new doctors and nurses or to putting more people on treatment for AIDS if resources suddenly dry up."

“We understand donors need reassurance that their money is well spent. But governments also need freedom to set priorities,” the minister said.

An action agenda submitted to the meeting called for more global solidarity, for example that industrialized countries adopt an ethical approach to recruiting health workers from developing countries.

Under the slogan: Train, Retain and Sustain, it called on African countries to improve training, compensation and working conditions of health professionals.

The agenda also urged governments to learn from the lessons of countries, such as Argentina, Brazil and Iran, on a number of workforce-related issues, for example: recruitment best practices for training and retaining a sufficient number of health workers.

Ministries of labour, finance and education — and not just health — should be involved in health workforce issues. Governments should seize the political momentum created by the Millennium Development Goals to promote their health and development agenda, it said.

There are an estimated 750 000 health workers for a population of 682 million people in Africa: 10–15

times lower than in OECD (Organisation for Economic Co-operation and Development) countries, according to two reports prepared for the Forum: *Addressing Africa’s Health Workforce Crisis: an Avenue for Action* and *Health Workforce Challenges: Lessons from Country Experiences*.

The region accounts for only 1.3% of the world’s health workforce but 25% of global burden of disease.

To achieve the Millennium Development Goals, the minimum level of health workforce density is estimated at 2.5 health workers per 1000 people compared with the current average of 0.8 health workers. Only six unnamed African countries currently have the minimum workforce capacity, according to the meeting documents.

“If we want a noticeable improvement in reducing maternal mortality rates and improving child health, then we have to have a higher density of health workers,” Kerstin Leitner, WHO Assistant Director-General for Sustainable Development and Healthy Environments, told the *Bulletin*.

Africa will require an estimated one million additional health workers to ensure the staffing required to deliver basic health interventions.

The two reports identified four key “hot buttons” responsible for the chronic shortage.

- Insufficient training opportunities. Two-thirds of sub-Saharan African countries have only one medical school, and eleven have no medical schools at all. There is too much emphasis on highly skilled personnel rather than other health workers.
- Deteriorating health of the workforce. In many sub-Saharan African countries between 18% and 41% of the workforce is already infected with HIV. In Zambia and Malawi, death of nurses represents almost 40% of the annual output from training, whereas in Ghana

there has been no noticeable increase in the health worker death rate.

- Rural/urban imbalance. In the United Republic of Tanzania, the city of Dar es Salaam alone has nearly 30 times as many medical officers and medical specialists as other rural districts. Only about five of Uganda’s 100 or so surgeons work outside urban areas.
- The “brain drain” of health professionals from poor developing countries like Ghana, Kenya, Malawi and Zimbabwe to higher-income developing countries such as South Africa and Botswana, and then on to richer countries such as Australia, Canada, New Zealand, the United Kingdom and the United States. An estimated 18 000 Zimbabwean nurses work abroad, whilst more Malawian doctors reportedly practise in the northern English city of Manchester than in all of Malawi.

At the same time, it is estimated that a further one million nurses will be needed over the next 10 years to meet the shortfall in the United States. By 2008, the United Kingdom will need 25 000 doctors and 250 000 nurses more than it did in 1997, and other

industrialized nations predict similar shortfalls. Bilateral agreements to regulate the movement of health workers have so far had limited impact.

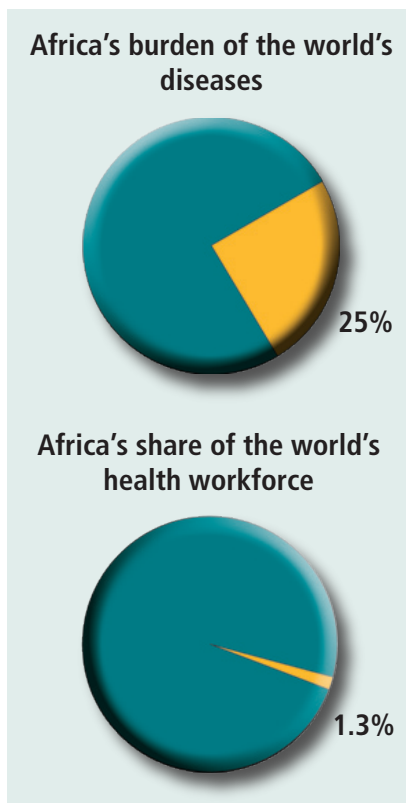
Leitner described the shortages as “staggering”, especially given the relatively high unemployment levels in some OECD countries.

She said there was a role for WHO in advising governments how to manage the migration.

“In terms of movement of people it

is a good thing to have health personnel with international experience, but this should not lead to a net reduction of health personnel in developing countries,” Leitner said. “At the moment it is a one way ticket.” ■

Clare Nullis-Kapp, *Cape Town*



Source: WHO

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*Nigerian Health Minister Eyitayo Lambo.*

## Health systems research is the best medicine

Every year millions of people die of diseases such as malaria and tuberculosis for which a cure has existed for decades. This gap — between knowledge and practice in public health — is at the heart of WHO-sponsored proposals to be considered this month by WHO's Executive Board.

The proposals, known as the Mexico Statement, call on governments, foundations and other bodies that fund research as well as the international research community to strengthen malfunctioning health systems by promoting more research into those systems.

Unlike previous research initiatives, the Mexico Statement calls specifically for more attention to be paid to research into health systems, for better ethical management of such research and better translation of these findings into public health practice.

"Research", the Mexico Statement says, "has a crucial but under-recognized part to play in strengthening health systems, improving the equitable distribution of high-quality health services, and advancing human development".

If the Statement wins Executive Board backing at a meeting in Geneva from 19 to 24 January, the World Health Assembly in May will consider adopting a WHO resolution that would commit signatory states more closely to the proposals.

The Mexico Statement was presented at a Ministerial Summit on Health Research in Mexico City, where 22 health ministers and other officials from 51 countries gathered from 16–20 November. Its goal is to tackle obstacles preventing low- and middle-income countries from achieving the Millennium Development Goals.

In a 12-point action plan intended to transform the way research is done and how its findings are disseminated, the Statement calls on governments to make research into health systems a priority; to give people in developing countries better access to knowledge and to base health policy decisions on scientific evidence.

It proposes establishing an international clinical trials register as one way of achieving these goals.

Although ministers agreed to "fund the necessary health research to ensure vibrant health systems and

reduce inequity and social injustice," their final statement stopped short of its original more concrete recommendation that developing countries should spend 2% of national health expenditures on health research.

A recommendation that development agencies allocate 5% of their health-sector financing for the same purpose ended up as a footnote. There were no specific proposals for industrial nations' contributions.

Dr Tikki Pang, Director of Research Policy and Cooperation in WHO's Evidence and Information for Policy cluster, said the Mexico Statement was vital because research into health systems tended to be neglected and under-funded in comparison with the field of biomedical research.

"Progress will only occur if countries show commitment and support for a spectrum of activities which will help to bring research into health system activities into the mainstream," Pang told the *Bulletin*.

The Statement won backing from officials attending the summit — a follow-up to a conference on health research in Bangkok in 2000 — but some delegates said it was too vague. Dr Elias A. Zerhouni, director of the U.S. National Institutes of Health, said translating knowledge into action was key but that the effective application of this knowledge was different in each specific context or local situation.

"The connection between policy-makers, leaders and evidence-based intervention needs to be strengthened by research," Zerhouni told the *Bulletin* before speaking at the Summit opening plenary session. "What we've also come to realize is that there isn't really a health research solution that is global in nature. Health systems are very local. What is effective in one system may not be effective in another."

If that is not taken into account, Zerhouni said, "what you have is a full disconnect between political leadership, policy-makers and deployment of health resources".

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*Dr Elias A. Zerhouni, director of the U.S. National Institutes of Health.*

Dr Lincoln C. Chen, Director of the Global Equity Initiative at the Asia Center of Harvard University and head of the Commission on Health Research for Development — the

1990 precursor to current efforts — said the proposals were not concrete enough.

Chen said that the past 14 years had seen a "huge revolution in developing countries coming up with research systems" but that he "would like to see something a little bit more specific".

WHO officials said the aim of the summit was to develop programmes and a methodology in four crucial public health areas: finance, workforce management, generating knowledge and managing supplies.

WHO's Pang argued that there were simple, cost-effective ways of making great strides for public health and cited the example of a district in the United Republic of Tanzania where child mortality was recently reduced by 46% after local officials re-directed part of their US\$ 2 per capita annual health budget into research to isolate the causes of child death and to addressing the underlying cause of the problem.

"It seems so obvious, and yet if you survey the literature it's very clear that very little attention is being given to this," Pang said, referring to health systems research, adding that since this involves human behaviour, society, economics, education and poverty: "It's just a very complicated area".

Dr Ariel Pablos-Méndez, Director of WHO's Knowledge Management and Sharing department, said the Mexico meeting underscored the need for a culture of knowledge translation and effective problem solving, new professional capabilities and different incentives in research systems in public health.

Pablos-Méndez said: "The Mexico Summit marks a shift in focus most timely and appropriate for the millions of poor people left behind, and offers a vision and a challenge to the international research community and national governments". ■

Theresa Braine, *Mexico City*