The newsletter of real action and research • **No. 2** • May 2005

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12-16 September 2005
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› Pandemic influenza

Pandemic flu remedies untested

SUMMARY

One day soon, flu could kill 100 million people. Most of the deaths will be in a developing world that is unprepared — and using unproven remedies.

› by Robert Walgate, Editor, *RealHealthNews*

Pandemic influenza is inevitable, and it may come soon. In the doomsday scenario, the highly pathogenic but difficult-to-catch "H5N1" bird flu now circulating in Asia will adapt to humans. Within three to six months, it is estimated, the whole world would be infected.

This bird flu has so far killed 51 of the 88 people it is known to have infected – a mortality rate of 56%. Their unusual symptoms are similar to those of the famous pandemic flu of 1918-20, an "H1N1" flu which is believed to have started in China and killed – according to modern epidemiological estimates – 50-100 million people.

The eight-gene RNA influenza virus constantly undergoes small mutations – but can also make large, sudden shifts in its genetic structure, where one virus exchanges genes with another, or "reassorts". In the doomsday scenario, H5N1 bird flu reassorts with a human flu virus, creating a strain equally virulent but far more easily transmitted between people.

Yet investigations by *RealHealthNews* in China, India, Nepal, Kenya, and Brazil – reported on our website – have revealed that lowest income countries and regions may be deeply unprepared for this event.

Meanwhile WHO – in the almost certain absence of drugs or vaccines for most of the world's poor – says that its recommended interventions, such as preventing public assemblies and imposing travel and trade restrictions, "may affect human behaviour and human rights". Moreover, it continues, "most of the interventions are based on limited evidence."

On our website *RealHealthNews* reports on the state of research in global preparedness for pandemic flu, and finds nearly 10-fold increases in investment in research in countries like the US – but to levels still not enough to create a polyvalent, pandemic flu vaccine, even by the end of the decade.

But if even that investment is too small, almost no research appears to be happening on how to protect the world's poorest and most exposed communities and countries. ■

www.globalforumhealth.org/realhealthnews/RealHealth.php

› Paromomycin to be registered

Kala azar cure for 2006

GLOBAL: The Institute for OneWorld Health announced on 14 April 2005 that they had won a US$10 million grant from the Bill and Melinda Gates' Foundation to complete the registration in India of paromomycin, an antibiotic, as a drug against visceral leishmaniasis (kala azar).

But there's also miltefosine, registered and trumpeted only a few years ago, and lipid-associated amphotericin B, and earlier drugs based on antimony.

So *RealHeathNews* asked Magriet den Boer, a pharmacist working for Médecins sans Frontières (MSF) on leishmaniasis in the Access to Drugs team: how important is it, do you think, to get a drug like paromomycin?

"Pretty important. Each of the existing drugs for leish has its own drawback, and there aren't very many, so it's a very valuable addition."

Amphotericin, said den Boer, has to be given by intravenous infusion, needing trained personnel, and even at cost price, it's still about US$400 per patient. "Otherwise it's a very good drug."

Miltefosine is very effective, and oral "which is great" – but the problem is that it is teratogenic [causes malformations in offspring].

"So we are very reluctant to give it to people, even to men, to finish it at home – because you never know what will happen. And it lasts a long time in the blood, so if a women takes it, for two months she should not get pregnant. It's a serious drawback."

And in Bihar, the poorest and the state most affected by kala azar in India, the old antimony drugs are now almost useless as the leishmania parasite has developed resistance. "So a new drug was very badly needed."

So MSF has been using paromomycin in small quantities, but it has never been properly tested. That's where IOWH came in. Registration will now be completed by the end of 2005 – and work and studies started to get it delivered, at US$5-10 per treatment, to the poorest who need it, largely through NGOs working in the hardest-hit areas of the world, like Bihar in India, and Sudan in Africa. **RW** ■

› **Read more** of the interview with Magriet den Boer, see the *RealHealthNews* web site, which you can reach through: **www.globalforumhealth.org/realhealthnews/RealHealth.php**

› Interview

Charitable drugs company will bridge rich and poor

RealHealthNews talks to Victoria Hale, CEO of the Institute for OneWorld Health

SUMMARY

Half-way house between a traditional pharmaceutical company and a charity, this institute is pulling in talent from Big Pharma, and while focusing on the world s poorest, aims eventually to break even with tiered pricing for the middle class. Its next jackpot: a back-to-basics malaria vaccine.

› RealHealthNews: In the Institute for OneWorld Health you are running a pharmaceutical company, yet we understand that you are not just going to register paromomycin for visceral leishmaniasis, but work out how to get it to those who need it!

Victoria Hale: We are with this drug, yes! This disease affects the poorest of the poor, who live very remotely. And there just isn't one organization or even one government that covers everyone. So we are assembling a group of parties committed to that disease and to that region to get the job done. It's not enough to get regulatory approval – you have to get the product to the people!

We're a not-for-profit, so we stand in the middle. We are a public charity; and we are a pharmaceutical company.

So we are a charity that produces new drugs, does new drug R&D, takes them through regulatory approval – and then

we would like to partner with large pharmaceutical companies to distribute drugs worldwide. But with this particular drug, in India, Bangladesh, Sudan, Ethiopia – some of these countries are not ones where we thought the pharmaceutical companies had a good distribution system. So we are working with NGOs, a little bit of private sector and certainly with governments in all of those areas. Putting together everybody.

› RHN: How does your economics work?

VH: We are funded by philanthropy right now. Almost all of our funding is from the Bill & Melinda Gates foundation. And with future projects – not with paromomycin but with future projects in malaria, diarrhoea, and some others, we expect to have sales not only to the poorest people but also to the middle class, to bring back some revenues, so we can become a self-sustaining organization. That's our model. But we are not for profit, so any funds that come back in revenue have to go into our next projects.

› RHN: There would have to be dual pricing, wouldn't there.

VH: Exactly. In fact multiple tiered pricing, we think, different in different countries and different in different sectors.

› RHN: Which will be a bit experimental, in the same country, won't it?

VH: It will be, but we are learning from our for-profit colleagues how to do this. This is done. We won't be the first.

› RHN: Are there any other organizations like yours?

VH: No… not that we are aware of. We have consulted with two companies that want to develop a non-profit vaccine organization, and one company that wants to develop diagnostics. But that's all so far.

› RHN: Tell us a little bit about yourself and your chief staff. Who are you, what kind of people are you?

VH: We're pharmaceutical scientists, primarily. I did a PhD in pharmaceutical chemistry, and then I went to work for the US Food and Drug Administration

(FDA); and then for Genetech; and then consulted for a few years for Genetech and a pharmaceutical company. Our other senior staff come from large and medium Pharma and biotech companies.

› RHN: Several of the Big Pharma people we've talked to in the last six months or so say they are really quite concerned about losing their staff to projects like yours…

VH: Exactly, I'll tell you!…

› RHN: …Quite a few seem to want to work on philanthropic projects.

VH: Exactly! There are staff that really feel that their hearts are no longer in their work. And to have an opportunity for a few years to do altruistic work is a great thing.

So many young scientists want to join us, and we have scientists who have decided to take an early out-package, or who have retired; and they are fantastic. We have an incredible culture. It's a very, very powerful spirit and they are very, very committed to the mission.

And do you know something? This feeling you describe runs throughout the pharmaceutical industry. So when you hear that some scientists want to leave, it really is true.

› RHN: So we may see some more clones of your kind of company!

VH: We may, that's right. I hope so. I honestly do. OneWorld Health can only do so much. We intend to partner with Big Pharma to take our projects further, but I'd like to see some variants on the model.

› RHN: What's your next big one?

VH: I would say it would be a malaria vaccine!

› RHN: No kidding! But that's so complicated, isn't it?

VH: But this would be back to basics. This is a whole sporozoite [the early stage of the parasite, as it first enters the bloodstream when a mosquito bites]. We're attenuating a sporozoite. Instead of complicated work with surface antigens, isolating them and producing them recombinantly, and mixing a few, let's just take the whole darn infectious organism!

› RHN: Well that's been proven to work a long time ago…

VH: It has been, you're right!

› RHN: …but the problem was growing enough, the culture of the organism.

VH: Well, we've got a pretty nice production system going now so we've overcome that, we believe! I'm serious. You'll hear more about that in the summer. **RW** ■

READ ON

Institute for OneWorld Health – a nonprofit pharmaceutical company
www.oneworldhealth.org/index.php

Announcement of funding of sporozoite malaria vaccine
www.oneworldhealth.org/media/details.php?prID=76

› Interview

Artemisinin combo tablet nears delivery

RealHealthNews talks to Bernard Pécoul, Executive Director of the Drugs for Neglected Diseases initiative (DNDi)

SUMMARY

DNDi signed a tough agreement in April 2005 with the pharmaceutical company Sanofi-Aventis, who will now manufacture and deliver by 2006 a fixed-dose artesunate-amodiaquine combination tablet developed by DNDi for half the malaria cases in Africa — at a price of under US$1. And from the start, it will be a generic medicine. How does DNDi work this magic?

› RealHealthNews: It was a surprise to be reminded that DNDi was working with malaria. Don't you focus on the most neglected diseases?

Bernard Pécoul: You know the definition of neglected diseases is quite wide. We started on artemisinin combination therapies (ACTs) for malaria in 2002… Before the existence of DNDi they were under the umbrella of Médecins sans Frontières (MSF), who were facing the lack of artemisinin combinations [for the now widespread drug-resistant malaria].

But the Medicines for Malaria Venture (MMV) had decided not to go into ACTs at that stage. They changed their minds in 2003, but during that first period they wanted to focus on new molecules. That's why we at DNDi were obliged to start this project in 2002, and now we are successful.

So we've developed one ACT which will be manufactured in collaboration with Sanofi-Aventis, and a second one – an artesunate-mefloquine – that we started with several partners. That is recommended mainly for Latin American and South-East Asia. Our aretesunate-amodiaquine is mainly recommended in Africa; 13 countries have switched the national recommendations to that, as well as in Asia.

› RHN: So how did you do it?

BP: First it was necessary to develop the new product. We spent more than two years to make it stable – it was quite complicated, because when you mix artesunate with amodiaquine, the amodiaquine produces water so the artesunate is diluted, and you can't maintain the right level for treatment. So the major obstacle was the pharmacology – we spent quite a lot of time on that – and the stability in tropical conditions. After that we did some studies in pharmacokinetics, and we are currently testing this new co-formulation in a clinical trial in Burkina Faso.

› RHN: Given that both components exist and are registered already, what do you need to do to get through regulation? Do you have to go through all Phases I to IV?

BP: It's a little bit special, so we've started to discuss with regulatory authorities. You can combine information from the non-fixed combination [the two substances in separate tablets, taken together] to apply to the fixed. So you can collect data on what has been used until now as a non-fixed combination, to complete with your new product.

We are confident that the dossier will be complete at the end of 2005. So we plan to have the drug available for patients in 2006.

The target price is US$1 per adult and 50 cents for a child. That was part of a long negotiation with Sanofi-Aventis, but one of the conditions was that they produce at cost. They've accepted that. The target price depends somewhat on the volume. But WHO is expecting that this combination will be used in more or less 50% of the cases in Africa, so we are talking about a huge volume of sales.

Their estimation of the need for ACTs is more or less 200 million cases a year. And the estimation for artesunate-amodiaquine is that 50% of the countries will use it.

Our product, when it's on the market, will substitute for the co-blister [packs of the two drugs as separate tablets]. Because the only choice for doctors and patients using this combination is to use co-blisters in a combination of 12 artesunate tablets with 12 amodiaquine. The risk is that that patients select only one, and in fact they select artesunate because artesunate has a very rapid effect – plus the taste of amodiaquine is not very good. [The concept of the combination is to reduce the rate at which malaria will develop resistance to artemisinin. Resistance will arise one day, but the day will be sooner if artemisinin is widely used alone.]

› RHN: And what price is the co-blister?

BP: Today it's US$1.6 – and it's produced by Sanofi-Aventis, and at least two generic companies from India.

› RHN: So will yours also be the cheapest single-tablet ACT?

BP: Yes, because the other is Coartem, artemether-lumefantrine, from Novartis at US$2.50.

And it will be much easier to use, because the formulation will be two tablets for an adult, once a day for three days.

You know this was a strong collaboration with MSF, WHO, and the UNICEF/UNDP/

Artemisia - in great demand but in short supply.

World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR).

All the definition of criteria came out of that: reducing the number of tablets, reducing the number of doses to once a day for three days – it was technically difficult, which is why it took a couple of years working with many different partners – with academic institutions, some biotech companies in Europe, helping us to find the solution.

› RHN: Here you have a nice new product – is it still necessary to continue research on new drugs for malaria?

BP: Of course, of course! I've been spending the last 20 years fighting against malaria. It's a parasite that's so capable of developing resistance, we cannot wait until the next resistance arises. It's why we are very connected with MMV, and it is very good news that they have some products in the pipeline. It would be catastrophic for the whole malaria strategy to depend on just a couple of combinations.

Plus you have different parts of the world, different situations… We are talking about 500 million cases a year!

› RHN: Another issue is ensuring the artemisinin supply…

BP: It's still a problem, but in the case of Sanofi-Aventis, they've tried to diversify their sources. They started with China, now they are making progress with a producer in Viet Nam, and they have also entered into negotiation with producers in Kenya, Tanzania and Madagascar.

Artemisinin comes from a plant that's quite easy to grow; but you have to plan in advance, it's a question of timing; it takes nine months, and then you have to have a good extraction capacity.

WHO and the Global Fund should plan solidly for future needs… [Their estimates] directly impact the production plan for our two fixed-dose combinations: artesunate-amodiaquine and artesunate-mefloquine.

› RHN: Who will own the rights to this combination?

BP: It took a lot of negotiation – but Sanofi-Aventis have accepted non-exclusivity in this agreement. So they've accepted that they will produce this drug as a generic. So as soon as the regulatory dossier is completed it will be available for other producers.

› RHN: So why ever did they agree to this? What's in it for them?

BP: Probably first of all the image of the company. And second because Sanofi-Aventis with this new large group they have quite a lot of products and are quite well-connected with Africa; so I think they want to maintain their presence in this market.

› RHN: And some companies are also having trouble retaining their scientists, aren't they, who want to work for good causes?

BP: Of course. I think they won't change their priorities – they will not change their agenda – but they will save money responding to that kind of issue. That was why it was so important for us to keep the possibility of working with others, particularly if this product will be so widely used. It will be very important to have several sources of the product.

› RHN: Is DNDi a public-private partnership (PPP)?

BP: I'm always a bit reluctant to talk about DNDi as a PPP, as we consider that leadership should come from the public sector. I prefer to have us defining the strategy, objectives and priorities, with the private sector involved in the implementation.

But what we do, on a not-for-profit basis, is try to develop a kind of virtual pharmaceutical company. On my team I'm the only one who hasn't had a long career with pharmaceutical companies. All the rest of my team have been managing products in industry.

› RHN: Do you get any funding from the Bill & Melinda Gates foundation?

BP: For the time being no. We have a relationship but we are not getting any money. But we are in touch. They are involved in everything, after all! ■

READ ON

DNDi agreement with Sanofi-Aventis
www.dndi.org/press_dossier01.asp

Medicines for Malaria Venture
www.mmv.org/pages/page_main.htm

TDR
www.who.int/tdr/

Roll Back Malaria
www.rbm.who.int

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› Indian patents

Indian patent law – a threat to generic medicines?

SUMMARY

Under obligation from the World Trade Organizations TRIPS agreement to recognize international patents, Indian law changed in March to restrict the development of new generic drugs, despite local and international protests. Existing supplies will be protected, but new drugs will not.

› by Bishakha de Sarkar

INDIA: The Indian Patents Amendment Act came into effect after it was passed by Parliament in March, 2005, but there are still loud murmurs of protest about the law, even though the government was forced to make severe changes to the original ordinance introduced last December.

Several of the more contentious aspects of the act were removed after a protracted opposition by Indian and global health activists, non-governmental organisations and left-wing political parties. But the activists fear that the law will increase India's disease burden, as well as that of the 350 000 HIV positive people worldwide now believed to be dependent on India's generic antiretrovirals – half of those on ARVs the developing world, according to Médecins Sans Frontières.

"Some of our apprehensions are very real," says activist Leena Menghaney. "The act is not clear on many counts," she says.

The act, which follows India's commitments under the international Trade and Intellectual Property Rights (TRIPS) agreement, changed a 35-year-old law to introduce product patents on drugs. So far, under the 1970 law, India granted patents on chemical manufacturing processes but not on the drugs themselves.

This effectively meant that an Indian company was free to break down a drug invented in a developed country and reproduce it using the same ingredients through a different process. These are the so-called "generic" medicines.

The now amended act states that a foreign government can still get generics from India, if the country has already been buying them, or by issuing a so-called "notification".

Prabir Purkayastha of the Delhi Science Forum (DSF) explains that all that a government needs to say is that it needed the drugs. And the present generation drugs reaching Africa would not be more expensive.

The sting comes in the future, as new drugs, produced from 2005, would come under the new patents regime.

The law allows Indian companies to reproduce generics patented up to 1995 – but not those after 2005. Companies that want to copy drugs and sell them more cheaply would need to file for "compulsory licensing".

It is this provision – which is intended to compel the patent holder to allow essential drugs to be made – that the activists fear leaves too many questions unanswered.

The law says that there will be a "reasonable" time period for the granting of compulsory licensing, but the activists stress that negotiations can last three years or more.

Though the proposed law makes provisions for a country facing a "national emergency", the Affordable Medicines and Treatment Campaign, a network of bodies based in Mumbai, holds that while the government may treat HIV/AIDS as a national emergency, it may not so recognize several other serious diseases – cancer

INDIAN PATENTS/ MSF ANALYSIS

Impact of Indian patent law is yet to come

The effects [of the Indian patent law] won t be immediate Daniel Berman, coordinator of the M dicins sans Fronti res campaign for essential medicines, told *RealHealthNews*. Because the way the law is written, drugs that were patented before 1995 are not impacted at all.

For drugs that were filed for patent, and put in what they call the mailbox , the patent office could go through those dossiers and grant some patents.

If they do decide to grant patents on those drugs from 1995 to January 2005, then the law says that those drugs already on the market in India would stay on the market.

The only thing that would happen is that the generic companies would have to pay a licensing fee to the patent holder. So there s no immediate change.

But in the long term, for drugs that are not yet on the market in India, the law gives a lot of power to the patent holder and it s going to be quite difficult for others to produce those drugs. **RW** ■

› **Read on** MSF's coverage of the future of Indian generics: **www.msf.org/content/page.cfm?articleid=A6DADC60-3036-44EA-A78B614146ACF5D8**

or high blood pressure, for instance.

Moreover, "Any of the major pharmaceutical multinationals can ask for an injunction to stop a compulsory license, while protracted litigation goes on," says Menghaney.

And new drugs – which will be needed to face rising drug resistance, and concerns about the side effects of old ones (see page 12) – are likely to be more expensive. The new law stipulates that generic drug-makers have to pay a royalty to the original manufacturers – without limiting its size. "We want it to be restricted to 4-5%, but if it is not specified, a company can ask for anything," says Purkayastha.

The DSF, which lobbied for the amendments that the government finally passed, stresses that the movement is far from over.

"We need a global movement against TRIPS," says Purkayastha. "The most we can expect out of an Indian Patents Act is the best of a bad TRIPS bargain. It is the bargain itself that needs to be challenged." ■

READ ON

People's Health Movement on the Patent Act
www.phmovement.org/india/articles/indianpatentact.html

Lawyer's collective - access to ARVs
www.lawyerscollective.org/lc-hiv aids/magazine_articles/april_2001.htm

Indian patent office
www.patentoffice.nic.in/ipr/patent/patents.htm

WTO's Doha Declaration on the TRIPS agreement and public health
www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm

Generics manufacturer Cipla's HIV Letter
www.cipla.com/whatsnew/CiplaHivLetter.pdf

Generics manufacturer Ranbaxy's HIV update
www.ranbaxy.com/aidonaids.htm

> Antiretrovirals from Africa: 1 of 3

Generics made in Zambia

SUMMARY

Zambia is to begin the manufacture of combination ARV treatments for HIV/AIDS, with a combination of Cuban and Zambian government and Italian management support.

> by Michael Malakata in Zambia, and Robert Walgate from new sources

ZAMBIA: Vice-President Lupando Mwape visited a refurbished pharmaceutical company in Lusaka, Zambia's capital, on 12 April – to congratulate it on manufacturing Zambia's first nationally-made antiretroviral drugs, according to reports in *The Times of Zambia* and *The Post* (Lusaka).

According to *The Post*, Pharco Pharmaceutical Company managing director Giovanni Leonardi said the first sales of the drugs are awaiting the successful completion of "clinical trials" [presumably trials to show bioequivalence to the proprietary drugs] on 28 HIV positive patients.

Late last year, IRINnews.org of the UN Office for the Coordination of Humanitarian Affairs reported that health minister Brian Chituwo had said: "We have managed to manufacture these drugs with assistance from the Cuban government, but we need to also sort out various regulatory issues and, also, there is need for verification from the World Health Organization (WHO) and also the [Zambian] Drugs and Poisons Board".

On 13 April The Post reported "[Vice President] Mwape yesterday confirmed that manufacturers had the ability to produce high quality products that would help to reduce the country's import bill".

Leonardi told *The Post* that the drugs – "Trimune", a combination of nevirapine, lamivudine and stavudine, would initially cost US$140 per patient per year, but the price was expected to fall depending on the cost of raw materials and production.

The Times reported that Mwape "hailed Pharco for the strides it was making in producing generic drugs – and challenged Zambians to buy the company's products".

Leonardi said the survival of Pharco depends on the government, which is the major buyer of drugs in the country to buy the locally produced drugs. Mwape said, however, that the Pharco's survival depends on purchases by the Zambian public – because they are the consumers.

"The tendency by Zambians to view locally manufactured products as being inferior is having a negative impact on the growth of the pharmaceutical industry in Zambia," Mwape said.

AIDS activists welcomed the news, reported IRINnews.

continuing on page 8 >

"We have been lobbying for affordable drugs for 10 years. This is a dream come true… our hope has not only been accessibility, but also affordable drugs. We also hope the supply will be sustainable, because once you take these drugs, it is for life" said coordinator of the Network of Zambian People Living with HIV/AIDS (NZP+), Clement Mfuzi, according to the IRINnews reports.

Pharco, an Italian company, was created in 1998 and started production in Zambia in 2000. It already produces antibiotics, anti-TB and anti-malaria drugs there. In 2004, Pharco decided to make ARVs – by upgrading its plant in Lusaka at the former Medical Stores premises, a government owned drug-manufacturing company.

"We are spending K2.5 billion [US$500 000] on the modernisation of the factory to meet WHO standards," said Leonardi, IRINnews reported.

One in every five Zambians is infected with HIV/AIDS – which has already claimed 700 000 lives since the first case was reported in 1984. The disease, according to Ministry of Health statistics, has orphaned 800 000 children in Zambia. Some 20% of Zambians – two million people – are living with HIV/AIDS.

The Times of Zambia last September reported that the Government's target was to have 100 000 people on ARVs by the end of 2005. This would be around a ten-fold increase over current numbers. ■

READ ON

allAfrica.com news service
allafrica.com/

IRINnews.org
www.IRINnews.org/

› Antiretrovirals from Africa: 2 of 3

WHO: African ARV production needs "big technology transfer"

SUMMARY

African governments are encouraging local production of antiretrovirals in fear of the Indian patent law, and as a matter of national pride. But countries need technology transfer and training to meet WHO s prequalification standards for generic medicines.

› RealHealthNews: A Zambian-based pharmaceutical company, Pharco Pharmaceutical, is gearing up to produce generic antiretrovirals (see page 8), and plans to sell to the Zambian government. Do they have a strong drug regulatory authority there?

Lembit Rägo, team coordinator for the Quality Assurance and Safety of Medicines, WHO: They have something, but probably the level and rigour of assessment that they can apply, given their limited resources, is limited.

› RHN: What's your feeling about making generic ARVs in Africa? There are several companies doing it now, aren't there?

LR: Well – I can tell you quite honestly what is my feeling because probably we know most about this business in the world! Because we run the prequalification programme for the UN family, and it's open to all manufacturers from all places.

We have gone through an impressive number of ARVs produced by the generic manufacturers, and if you look at the prequalified list [see READ ON below], it's quite limited. So this means that a lot of them have failed. And we know the reasons for the failure, too.

For example, we had one not very developed African country where the government wanted us to assess their potential to manufacture ARVs. Which in fact they were already doing. And they asked us to assess six manufacturing sites. And our experts concluded that none of them is fit to do the job properly… None of them had sufficient experience how to formulate generic drugs properly.

› RHN: What's the solution to this?

LR: As usual there are no good solutions for complicated problems, otherwise they would not be complicated! There's a lot of politics involved.

Many African countries now fear the change in the patent situation in India (see page 6). They are worried that the Indian companies who have been providing them with affordable generic drugs, may no longer be able to do that. So they all now want to start their own national production.

A lot of national pride is involved, and emotion; but sometimes the projects are neither financially viable nor professionally viable. They are politically driven processes.

In India, at least, there are manufacturers who can do the job properly, because

they are quite big companies that can invest resources and do the business. If they are pressed to do it they can do quality production, no problem.

But the small companies in smaller countries may face extreme difficulties unless there is big technology transfer – and considerable support in technical knowledge and expertise, and finance to upgrade the facilities.

Factories may not even meet good manufacturing practice standards, they may need upgrading, and investment.

Even in Europe, if you are a company deciding "I want to make the generic drug, X", and you start today, to do it properly it takes you at least one year. And sometimes we have seen that these smaller production units have products popping up in six months, which means that they haven't done everything necessary.

› RHN: Are the molecules in ARVs quite difficult to make?

LR: Not all of them. There are a lot of molecule-specific problems. Some are easier to formulate, some trickier.

› RHN: The Zambian one is called "Trimune": nevirapine, lamivudine and stavudine.

LR: Triple combinations are more difficult to do.

› RHN: Have they applied to you for prequalification?

LR: I don't think so. Not yet, to my knowledge. **RW** ■

READ ON

List of prequalified manufacturers for drugs and diagnostics for HIV/AIDS
mednet3.who.int/prequal/hiv/hiv_suppliers.pdf

The WHO prequalification project
mednet3.who.int/prequal/

› Antiretrovirals from Africa: 3 of 3

Check the quality, cure the disease

SUMMARY

Generics are crucial, but for antiretrovirals against HIV/AIDS, as for any pharmaceutical, it s essential for purchasers to ensure quality, says M decins sans Fronti res (MSF).

› RealHealthNews: Several companies in Africa are beginning to make generic anitretrovirals (ARVs) for HIV/AIDS now. If you are buying, what should determine your choice of manufacturer?

Daniel Berman, coordinator of the MSF campaign for essential medicines: I think the most important thing is to ensure that they are meeting international quality standards. So in a place like South Africa [where Aspen Pharmacare make ARVs], that's fairly straightforward, because they have a strong regulatory agency.

But in a country without a strong regulatory authority, an option for making sure the quality is good is to apply to the WHO's pre-qualification programme [see page 8]. That way they can have professionals come to their plant, look at the dossiers, and put their stamp of approval on the drug.

MSF strongly supports the use of generics. But the drugs must meet certain standards.

The challenge for buyers is to make sure that the drugs are of high quality.

This is not a problem that's unique to AIDS, it applies to any type of drug. For example in Asia, a considerable percentage of the artemisinin drugs on the market do not meet the standards

› RHN: You mean they just don't contain the quantity of active ingredient on the label?

DB: Right, right. So what we do at MSF, if we are going to use drugs produced locally, is to go through an internal quality evaluation process; but we wouldn't necessarily do that if there was a drug already available at a good price from one of the companies that has already met the standard.

› RHN:What advantage would there be to having ARVs produced in Africa? Could they be produced more cheaply? Or are generic prices at rock bottom production level now?

DB: I don't think so much it's where they are being produced, it's the quantities [that determine price]. So companies like Aspen Pharmacare in South Africa or Cipla and Ranbaxy Laboratories in India have huge volumes, so they probably have the lowest costs per unit; and they are already working in places where the labour price is low. **RW** ■

READ ON

MSF essential medicines campaign
www.accessmed-msf.org/

Aspen Pharmacare Holdings
www.aspenpharma.com/

Cipla
www.cipla.com/globalpresence/globalpresence.htm

Ranbaxy
www.ranbaxy.com/

› Nevirapine: 1 of 3

US experts back nevirapine to halve mother-to-child HIV transmission

SUMMARY

The controversial Ugandan HIVNET 012 trial of single-dose nevirapine for mothers and babies has finally been vindicated — in a definitive study by the US Institute of Medicine. But government and media silence on the story in South Africa could deepen public anxiety about AIDS treatments, warn experts.

› by Tamar Kahn

SOUTH AFRICA: The health authorities and the local media appear to have largely ignored the recent study by the Institute of Medicine, one of the US National Academies, confirming the findings of a pivotal Ugandan trial of the safety and efficacy of nevirapine – the drug most commonly used in the developing world for prevention of the transmission of HIV from pregnant women to their babies (PMTCT).

The 1997 Ugandan trial, called HIVNET 012, has been dogged by controversy over the way records were kept and the conclusions drawn by the researchers. The drug trial investigated the safety and efficacy of a single dose of nevirapine given to the mother during labour, and another to the baby shortly after birth. The researchers found that single dose nevirapine cut the risk of an HIV-infected mother passing on the virus 50%.

"None of the shortcomings that we discovered upon reviewing the data and conducting our own original analysis of source documents indicates a need to retract or discount the study's findings," said James Ware, chairman of the committee authoring the IOM report.

Since 2000, drug resistance to nevirapine began to be observed, but according to WHO guidelines "The concern about resistance should be balanced with the programmatic simplicity and practicality of the single-dose nevirapine regimen compared with other regimens and the urgent need to expand programmes to prevent mother-to-child transmission".

WHO issued its own support for the Ugandan trial in July 2003.

Yet senior officials at South Africa's medicines regulatory authority, the Medicines Control Council, and Health Minister Manto Tshabalala-Msimang have previously said the Ugandan study was cause for concern. And the December issue of ANC Today, the online news bulletin of the ruling African National Congress, also questioned the safety and efficacy of the drug.

Neither the health department nor Medicines Control Council issued statements following the Institute of Medicines Report.

This week (18 April) the health department's spokesman Sibane Mngadi referred queries to the Medicines Control Council (MCC), which failed to return calls.

South Africa's most influential AIDS activist group, the Treatment Action Campaign, said it was "unacceptable that neither the ANC nor the Health Minister had told the South African public about the findings of the Institute of Medicine study".

"It's unfortunate that in South Africa, unless there's bad news on nevirapine the stories don't go out..."

"It's unfortunate that in South Africa, unless there's bad news on nevirapine the stories don't go out. The media isn't interested, and government and the MCC can't say I told you so," said Glenda Gray, one of South Africa's leading researchers on the prevention of mother-to-child transmission, and co-director of the perinatal HIV research unit at Chris Hani Baragwanath Hospital.

She said the Institute of Medicine "affirmed the norm", but the South African government needed to move on from single dose nevirapine to more effective treatments.

The concern among health workers and researchers about the authorities' current silence on the safety and efficacy of nevirapine stems from their experiences of dealing with anxious patients – when senior officials and politicians have previously voiced concerns about the drug.

Despite their silence, South African health facilities in eight out of nine provinces do provide single dose nevirapine to HIV positive pregnant mothers and babies. The Western Cape province uses a different drug regimen, that adds a short course of AZT to the nevirapine treatment.

Following the 15th International AIDS conference in Bangkok, where researchers presented studies highlighting

possible drug resistance in mothers who had received single dose nevirapine, the South African Health Minister set up a committee to reconsider the country's drug treatment guidelines for preventing mother to child transmission of HIV. Eight months later, it is unclear how far the committee has progressed with its work.

Healthcare professionals are now battling AIDS drug fears among their patients on a new front, as a controversial US-based vitamin salesman, Matthias Rath, has launched a widespread media campaign to discredit the life-prolonging medicines. Using newspaper advertisements, pamphlets and flyers, he and his Dr Rath Health Foundation are spreading the confusing message that vitamins alone can cure HIV, and that anti-retroviral medicines are toxic. The local Advertising Standards Authority has ordered his advertisements to be withdrawn, but so far none of the health regulatory authorities (such as the MCC or Health Professions Council) have intervened. The Treatment Action Campaign will be in court next week (26 April) in an effort to stop Rath's activities, and have threatened to sue the MCC and Health Professions Council if they do not stop Rath's activities. ■

READ ON

The Institute of Medicine's statement
http://www.iom.edu/report.asp?id=26287

The Treatment Action Campaign's homepage
http://www.tac.org.z

WHO support for the Ugandan trial
http://www.who.int/reproductive-health/rtis/nevirapine.htm

› Nevirapine: 2 of 3

"We are happy" with scientific backing says Ugandan Health Minister

The Ugandan Minister who approved the use of nevirapine to slow mother-to-child HIV transmission is delighted with confirmation of his trust in his scientists

› by Peter Wamboga-Mugirya

UGANDA: "We were happy that Uganda's study on nevirapine for PMTCT has been vindicated by the US Institute of Medicine as being safe and well-administered" Uganda's Junior Minister of Health, Capt. George Mike Mukula, told *RealHealthNews*.

"This has confirmed our position that we're right. We are now expanding PMTCT, as it is most successful on lowering HIV prevalence in new-borns."

The number of Ugandan pregnant women accessing nevirapine to prevent mother-to-child-transmission of HIV reached over 600 000 by end of 2004.

Saul Onyango, the Coordinator in charge of the Care and Support Unit for PMTCT, told *RealHealthNews* that public response is rapidly scaling up. Over one million women get pregnant in Uganda annually, and since the year 2000 when the PMTCT was launched, a total of 627 000 pregnant women have accessed the services, 299 000 accepted voluntary testing and 30 775 were found HIV-positive.

"By the end of 2004, 16 700 of the voluntary-tested women got nevirapine treatment, while 10 400 nevirapine babies were born," says Onyango.

When nevirapine came under attack (see page 10), Capt. George Mike Mukula told *RealHealthNews*, Uganda did not stop administering nevirapine – because he believed the country's top medical researchers on the trial – principal investigators Francis Anthony Mmiro, Philippa Musoke and Laura Grey – "had done an excellent job" in testing the drug.

"I myself approved its use on behalf of the Ministry of Health and indeed the Government of Uganda, after the two of our best medical scientists certified its safety and efficacy. Today, there's clear evidence that nevirapine prevents infection in new-born babies" Mukula said.

Phillipa Musoke was quoted in the local media last December as saying the introduction of the drug had been a major breakthrough for the prevention of HIV to the unborn babies in the developing countries, despite creating resistance in a few mothers and children.

According to Mukula, Asian and other African countries, such as Thailand and Zambia, have sent medical teams to study Uganda's success with PMTCT. ■

› Nevirapine: 3 of 3

"No toxicity" in nevirapine PMTCT

SUMMARY

Warnings about nevirapine liver toxicity apply only to long-term use, in drug combinations.

› by Kimani Chege

KENYA: Nevirapine remains the drug of choice for the prevention of mother-to-child transmission of HIV in East Africa, despite a warning from the US Federal Drug Administration (FDA) earlier this year that the drug could cause liver damage.

In its public health advisory on the drug, the FDA said "In spite of the potential for serious and life-threatening liver toxicity and skin rashes with nevirapine, there are multiple reasons why nevirapine remains an important part of an HIV treatment regimen for many HIV-infected individuals world-wide."

Moreover, the FDA continued, "symptomatic liver toxicity has not been reported with the use of single doses of nevirapine to the mother and to the child for prevention of peri-natal HIV infection".

When the advisory was released, governments in the East Africa region rushed to affirm their trust in the drug, which is free to prevent mother-to-child transmission (PMTCT), easy to use, can be stored at room temperature, and reduces transmission of HIV by half, according to a Ugandan study now backed by both WHO and the US Institute of Medicine (see page 10).

Boehringer-Ingelheim, who manufacture the drug and provide it free for PMTCT to public health authorities and NGOs in 57 countries, issued the original warning, alerting the FDA, but a company spokesperson told *RealHealthNews* that the toxicity only arose if nevirapine was taken regularly as part of a cocktail of anti-HIV drugs. Several clinical studies of the single-dose treatment to mothers and babies, such as the South African SAINT study, showed "not a single indication" of toxic effect, she said.

"But we do recommend that it is given as part of a complementary programme to treat the mother for HIV/AIDS", she said, so the mother is not just left to die.

WHO also confirmed to *RealHealthNews* that a single oral dose to a mother during labour and a single oral dose to the infant within 72 hours after birth, remains a recommended treatment to reduce MTCT.

Ninety per cent of Kenyan children infected with HIV arise as a result of mother-to-child transmission with infection occurring during pregnancy, labour, delivery and breast-feeding.

In Kenya the drug is administered in combination with other drugs, but the Kenyan health officials through the National AIDS and STIs Control Programme (NASCOP) issued a statement noting that there would be no shift in policy regarding the use of nevirapine.

In the statement the officials said that the country strictly administers the drug to female patients who have a CD4 cell count of below 250, following the FDA advice. According to the FDA, nevirapine liver toxicity is less than 2% for both men and women with CD4 count of under 250.

While this raises the question of how CD4 counts can be measured in poor settings, Sylvia Ojoo, a clinical specialist and an anti-HIV therapy programme officer with NAS- COP says that nevirapine remains a choice for most Africa countries due to its affordability and its ability to be taken in fixed dose combinations.

Noting that Kenya did not choose inferior drugs, she says researchers in Kenya have analysed over 2 000 patients and only 2% showed some form of complications on using the drug.

"We are running a national programme that needs to draw in consideration cost, ease of use and effectiveness. Our choice of nevirapine was based on data collected over time both in developed and developing countries," Ojoo told *Real HealthNews*.

Noting that incorrect use of any ARV drug would result in complications, she calls for the strengthening of national antenatal care to enable women to use any preventive drugs effectively.

She insists that nevirapine has proved to be very effective in expectant mothers once either combined with D14 and 3TC or AZT. "We will continue to use the drug until other solutions come up." ■

READ ON

FDA public health advisory on nevirapine
www.fda.gov/cder/drug/advisory/nevirapine.htm

South African Intrapartum Nevirapine Trial (SAINT) Results

Journal of Infectious Diseases 2003; 187:725-735

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RealHealthNews is supported by the Global Forum for Health Research. Views expressed are not necessarily those of the Global Forum.

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