WHO to launch first essential medicines list for children

WHO's list of essential medicines turns 30 this year and will finally have an offspring: a parallel list of essential medicines for children that specifies proper dosages and formulations for their smaller, constantly-changing bodies.

A list of essential paediatric medicines is sorely needed. The WHO essential medicines list, first launched in 1977, is predominantly for adults. It includes some dosages for children, but in most cases formulations for children simply do not exist.

Children cannot be treated as “little adults” when it comes to medicines. “Children differ in the way they ingest, absorb, metabolize and excrete drugs, and behavioural and developmental issues complicate their treatment,” said the United Nations Children's Fund (UNICEF) and the World Health Organization (WHO) in a report last year.

The report concluded: “These factors are not constant but vary as the child grows. The majority of medications worldwide are not formulated for easy or accurate administration to children.”

An estimated 10 million children die every year, many from diarrhoea, malaria, respiratory tract infection, pneumonia or HIV/AIDS. Medicines for these illnesses exist, but paediatric formulations and knowledge on how best to use them in children are often lacking. To remedy this, WHO, UNICEF and others proposed a paediatric essential medicines list at a meeting in August 2006 in Geneva.

WHO has since developed a draft list of medicines and distributed it, setting a 30 April deadline for feedback. A committee of experts will finalize the list at a meeting to be held from 9 to 13 July.

The list will be made available to countries by September or October and will undergo revision as more children's medicines become available.

It would not be the first list of its kind – Canada, the United Kingdom, the United States of America and other developed countries have their own versions – but it would be the first to address diseases of children in developing countries.

The project is timely given a number of factors. The changing nature of childhood diseases is one. Children today need more chronic treatment than in the past, when health systems mainly had to manage children with acute diseases for which some medicines exist.

Secondly, the world’s health systems and public health organizations are making a concerted effort to deal with malaria – which accounts for one in five of childhood deaths in Africa alone – and other major infections, such as HIV, in children. But there are few age-appropriate formulations for antimalarials or antiretrovirals.

Thirdly, the USA and the European Union have acknowledged the lack of children's medicines in developed countries and are seeking ways to address it from a regulatory perspective. At the August 2006 meeting, experts from WHO, UNICEF and other organizations took stock of existing children’s medicines and their availability. The meeting’s report found that of 284 medicines on the adults’ list, 119 required an approved indication for use in children. While 52 of the 119 had a paediatric formulation listed, the remaining 59 did not. There were eight duplicate listings.

Certain diseases are common in childhood, such as meningitis, pneumonia, ear and respiratory infections, and gastrointestinal infections. “You might need additional drugs that you wouldn’t use in adults,” said Dr Suzanne Hill, a scientist from WHO’s Policy, Access and Rational Use team.

“What we’ve not had is a separate list that covers comprehensively all the diseases of childhood,” Hill told the Bulletin. “And we certainly haven’t looked in detail at medicines for neonates.”

HIV infection and malaria are diseases in adults too, but the dosage for the medicines used to treat them is different for children. On the existing essential medicines list for HIV, there are 12 antiretrovirals with syrup formulation, which can be used in children. But dosage forms that combine antiretrovirals in one tablet would be more appropriate, as children usually need to take three or four drugs at a time.

Research is just beginning into many paediatric medicine formulations and it’s no small task. “Several hundred medicines need to be evaluated as to whether they should be on the children’s essential medicines list,” said Dr Howard Zucker, assistant director-general of WHO’s Health Technology and Pharmaceuticals cluster of departments.
Dr Jane Schaller, executive director of the International Paediatric Association in British Columbia, Canada, said that drugs on the list need to be affordable, and take into consideration distribution and storage. Many existing formulations need to be refrigerated, which is difficult in places with unreliable electricity supplies, Schaller said.

Not all adult medicines are palatable to children. For example, zinc is an effective treatment for diarrhoea in children, but children don’t like the existing tablet formulation and refuse to take it. Kids often dislike syrups too.

What’s needed is solid-dose formulations that a child can swallow, Hill said. “We know they work, they’re on the essential medicines list, but we need to have a dose and a formulation that is palatable to children,” she said. “And we need a manufacturer who will make that and do so at a reasonable price. So that’s the sort of process we’ll be going through for all the different diseases.”

Developing medicines for children requires clinical trials. An important part of researching adult medicines to enable their use in children will involve looking at side-effects. Currently there is very little information on adverse drug reactions in children. Trials involving children—who can be more vulnerable than adults—need to done according to the highest possible standards with close monitoring.

Several companies and research organizations are doing clinical trials in children. GlaxoSmithKline is studying chewable asthma tablets, ointment against impetigo in children aged 1 month to 1 year, and drugs to combat HIV/AIDS. Other trials include a study of the use of lithium in treating paediatric mania by the National Institute of Child Health and Human Development at Case Western Reserve University in the USA, and Pfizer’s comparison of adults’ versus children’s doses of a drug for ear infections.

The big question is how to encourage pharmaceutical companies to start costly and often challenging trials for a whole new series of children’s medicines, when the markets for these medicines are mainly in developing countries with small health budgets.

UNICEF has proposed an advocacy plan to promote the development of such medicines. WHO has a prequalification programme: a list of medicines it recommends for purchase by United Nations agencies for developing countries, which also serves as a market incentive, Hill said. She added that this system had successfully encouraged generic manufacturers to produce high-quality, affordable medicines for adults.

“Our challenge at WHO is to work with Member States on this comprehensive approach to improve medicines for children and make them available, in the right dose and form, for the right purpose, to improve children’s health.”

Dr Suzanne Hill, scientist from WHO’s Policy, Access and Rational Use team.
Making malaria deaths easier to count

Autopsy for medical purposes is illegal in Rwanda, so it is difficult to know how many people die of a specific disease. But a change in the law expected this year has spurred researchers to establish Rwanda’s first postmortem programme that would start by helping with one of the most difficult of diagnoses in children: cerebral malaria.

As the only Rwandan pathologist in his country, Dr Eugène Mutijima is unique in many ways. Not only does he provide much-needed diagnostic support to clinicians at hospitals in Rwanda – saving these institutions from sending scant funds on outsourcing abroad – but he is also unusual among African medical graduates in choosing to work in his home country after training in Europe.

If a new medical research bill is passed this year as expected, Mutijima may soon be helping doctors in his country diagnose cerebral malaria and ascertain how many children actually die of this, the severest form of malaria.

One of those doctors, Professor Cyprien Baribwira, from the Paediatrics Department at the University Hospital in Kigali, explained that this research project has a vital public health purpose. It will certainly improve treatment. “When one knows the causes of death, one can improve treatment. But when one does not know, one cannot,” Baribwira told the Bulletin.

Mutijima has been re-establishing the Pathology Laboratory in Butare, about 130 km from the Rwandan capital of Kigali, since returning to his native country last year following five years of specialist training at Belgium’s Liège University.

In his laboratory, Mutijima, head of the Pathology Department at the University Hospital of Butare, analyses pathological specimens from people admitted to the country’s two main public hospitals as well as all the private and some district public hospitals. But despite his training, Mutijima is unable to ascertain specific causes of death in many of these cases because under current law he cannot perform full autopsies in order to do this. (See Malaria deaths are the hardest to count, Bulletin of the World Heath Organization 2006; 84(3): 165–6.)

Cerebral malaria is responsible for many deaths among children in Rwanda and is fatal within days unless treated. But symptoms are ambiguous and resemble those of several other illnesses including bacterial meningitis, Mutijima explained.

The standard diagnostic test for malaria is a blood smear to detect the parasites. Some centres have rapid diagnostic test, but these do not differentiate between cerebral malaria and other causes of neurological syndromes in children who have incidental parasitaemia. “In many cases the only way to understand what happened to the children is by autopsy,” Mutijima said.

The only autopsies currently allowed in Rwanda are those mandated for legal purposes. However, Mutijima and his colleagues expect this situation to change when a bill containing proposals to allow medical autopsies, is passed in coming months.

The new legislation, which will be unique among countries of Africa’s Great Lakes region, would enable Mutijima, in collaboration with Liège University neuropathologist Dr Manuel Deprez in Belgium and paediatricians Bariwira and Dr Cwinya-ai Neniling in Rwanda, to start the country’s first study of child deaths.

Their hope is that results from this work will help improve care for children with febrile encephalopathy of which Plasmodium falciparum malaria is a major cause.

The crux of the study, which is currently under discussion by the ethical review board in Rwanda, is to follow all children hospitalized with febrile encephalopathy. They plan to use their clinical and pathological findings to identify potential risk factors for poor prognosis and features that could improve diagnosis.

The first phase of the project, a large retrospective review of paediatric charts by Bariwira and Cwinya to identify the clinical profile of children admitted to hospital with febrile encephalopathy, is already under way. And once the law is changed, additional autopsy data will move the research forward by enabling the researchers to establish pathological correlates for their clinical findings.

Family consent is mandatory for medico-scientific autopsies such as these and sociocultural considerations.
are key to gaining parents’ trust for this work. This is especially true for autopsy, which is controversial in Rwanda because it recalls all-too-recent memories of mutilation during the 1994 genocide.

Baribwira, who was involved in drafting the medical research bill, said that as in other African countries parents do not want scars left on their children’s faces. He added that other countries’ experiences show that relatives may be reluctant to wait the necessary four to six hours after death for an autopsy, preferring instead to hold the funeral as soon as possible.

According to Mutijima, these difficult social responses are reflected in their colleagues’ mixed reactions to this project after it was presented at the annual Rwandan medical congress last September in Butare. “Some think that it will be impossible because of sociocultural considerations, but others have confidence in it. It is a big challenge,” he said.

Baribwira believes that despite the cultural sensitivities, parents will respond to the chance of an accurate diagnosis through autopsy, and that this project will fulfill a great need in paediatric research in Rwanda. It is common for parents in rural areas to blame poisoning or supernatural causes for their children’s disease, he said. An accurate diagnosis is therefore important to “de-dramatize the situation” and to reinforce public health messages about prevention.

“I am convinced that autopsy in the context of a hospital with limited means of diagnosis is an important additional tool to help us meet our responsibilities to parents and patients,” Baribwira said. “If we continue not to know what some of our children die from, and assume that the facts we have are good, we will never be able to advance to save the other children,” he added.

The research project has received a strong vote of support from Rwanda’s minister of state for infectious diseases and AIDS, Dr Innocent Nyaruhirira. But Mutijima said that despite this recognition there are still problems finding funds to cover the cost of the equipment. “We need to establish the autopsy room, which is very expensive. We are trying to look for financial support from the Ministry of Health,” Mutijima said.

The project will form the basis for Mutijima’s doctoral thesis, but the wider goal is to establish the practice of autopsies in Rwanda and make an international clinico-pathological centre of reference in cerebral malaria. “It is a big challenge,” he said, “but I think the work will have a good impact on the management of febrile encephalopathy”.

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The female Anopheles mosquito acts as the vector for malaria. It carries malaria parasites after sucking infected blood from humans and can transfer these parasites to other humans when it bites them.