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Vaccines and medicines for the world's poorest

Public-private partnerships seem to be essential

Three million children die every year in poor countries from diseases that can be prevented by vaccination.[1] Millions more die from diseases—like malaria and AIDS—that should be preventable by vaccines if they were developed. Unfortunately existing vaccines are not reaching these children because of failures in delivery systems, lack of resources, and the high price of some newer vaccines. Moreover, new vaccines may not be developed because private companies can't foresee a good return. The same story of huge need and market failure applies to drugs: of 1223 drugs developed between 1975 and 1997 only 11 were for tropical conditions.[2]

The problems seem huge. Yet there was an upbeat end to a meeting on the problem in Carmel, California, last month organised by the Institute of Global Health and the Global Forum for Health Research. The issue is rising up political agendas around the world, and new public-private partnerships are being devised to increase access to vaccines and drugs and develop new ones. Reducing deaths from communicable diseases would be a rich prize because these account for three quarters of the mortality gap between the rich and the poor world.[1]

Although the meeting ended optimistically, the problems at the moment are getting worse. The AIDS epidemic in the developing world is spiralling out of control, with India, for instance, on course to develop the high prevalence seen in subSaharan Africa. Malaria is in danger of becoming untreatable, and drug resistant tuberculosis is spreading.

A global approach is needed to tackle the problems. International organisations must coordinate efforts. Rich countries need to recognise their responsibility to contribute resources. Poorer countries must change their health systems, and some—like India—should probably increase their investment in health. Recognition is growing, particularly in the World Bank, that investing in health is one of the best ways to counter poverty and promote economic development.

Similarly the public and private sectors will need to work together in new ways to make vaccines and drugs available to the world's poor. The public sector alone cannot solve the problem because almost all new vaccines and drugs come from private companies. Yet private companies cannot solve the problem alone because their obligations to their shareholders mean seeking the highest returns—which tend to come from developing products for the rich world.

There are two main ways in which new vaccines and drugs for the poor world might be produced: "push" mechanisms that reduce the cost of producing new vaccines and drugs, and "pull" mechanisms that increase the market for them. Push mechanisms include public funding for research into the diseases of the poor, research tax credits for companies, help with development of new products, funding for clinical trials, and making it easier to register new products. Pull mechanisms include commitments to purchase new products once they are developed, tiered pricing (whereby the rich pay more than the poor), and tax credits on sales. Evidence must be gathered on the effectiveness or otherwise of the various mechanisms.

Many public-private partnerships are emerging that use a combination of these mechanisms. One of the best known is the International AIDS Vaccine Initiative, founded in 1996 with money from governments, corporations, and foundations (including those of Rockefeller, Bill Gates, and Elton John). It works by increasing public support for an AIDS vaccine, advancing the science, and encouraging industrial participation in vaccine development. It loans money to biotechnology companies with good ideas and helps manage research and development, usually putting together a biotechnology company, a development group, and a developing country.

The South African AIDS Vaccine Initiative, which has links with the international initiative, is a public-private partnership that aims to have an AIDS vaccine for southern Africa by 2005. The Medicines for Malaria Venture aims to produce a new antimalarial

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The full text of a draft consensus statement sent to the White House from the Carmel meeting appears on the BMJ's website

drug every five years. Founded because the pharmaceutical industry had withdrawn from the malaria market, the venture funds research and will manage development and production under licence. Pharmaceutical companies have donated compounds that might be developed into useful drugs. These partnerships build on the experience of many established programmes and have been joined by the Global Alliance for Vaccines and Innovation, which has funds from Bill Gates and other sources, including industry, to deliver vaccines to poor children.

Perhaps because of some of these new partnerships, governments are also becoming more interested in this issue. President Clinton has made budget proposals that would substantially increase the United States's expenditure on the problem. He is proposing $50m (£31m) for the Global Alliance for Vaccines and Innovation; a large increase in research expenditure on malaria, tuberculosis, and AIDS; a $400m (£250m) increase in health funding to poor countries; and a $1bn (£625m) tax credit on sales of new vaccines for diseases that cause over a million deaths a year (the *BMJ*'s website has the full text of a memorandum from the Carmel meeting to the White House). This package may well pass through Congress, particularly now that four US pharmaceutical companies have agreed to donate $150m (£94m) worth of vaccines through the alliance.[3] The World Bank is proposing to create a permanent £1bn fund for vaccines, partly because it is so convinced that paying for vaccines is one of the best ways of relieving poverty. Tony Blair is personally interested in the problem, and Britain has put money into several of the partnerships. The European Union has talked rather than acted, but perhaps it will want to join the worldwide initiatives.

Public-private partnerships may not solve the so far intractable problem of getting vaccines and drugs to the world's poor—and politicians may lose interest. On the other hand, the combination of good ideas on what to do and commitment to do something might mean that millions of unnecessary deaths and much suffering in the poor world could be prevented.

Richard Smith *editor BMJ*

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Managing status epilepticus

New drug offers real advantages

Status epilepticus is a medical emergency familiar to accident and emergency departments, acute medical wards, and intensive care units. It is defined as a continuous seizure lasting for at least 30 minutes,[1] or two or more discrete seizures between which the patient does not recover consciousness, and in the 15-30 patients per 100 000 per year who present in status epilepticus mortality may be as high as 10%. The longer seizures persist the more difficult they are to control and the higher the mortality,[2] with an increase in neuronal damage and chronic epilepsy. Until recently phenytoin has been the drug of choice for managing prolonged seizures, but it has to be given intravenously and major side effects are common. Fosphenytoin is a prodrug of phenytoin, recently licensed in the United Kingdom, that seems to offer several advantages over its parent.

Status epilepticus is challenging to treat and may be difficult to diagnose. In early status epilepticus patients usually have visible tonic-clonic seizures, although motor-convulsive activity can decline. Diagnosis may require electroencephalographic monitoring, because some patients have seizure discharge without detectable motor activity. An electroencephalogram is also invaluable to exclude "pseudostatus epilepticus," which is seen more commonly in specialist neurological practice. Early treatment of status epilepticus means easier control, and basic life-support measures should not be ignored. Initial treatment of the patient should include the appropriate management of airway, breathing, and circulation and measurement of glucose and blood gases. Metabolic causes of seizures should be reversed as a priority. Emergency departments should have established protocols for dealing with this medical emergency.

If control of status epilepticus is delayed epileptic activity may outstrip metabolic capacity and glucose delivery, and metabolic and hypoxic-ischaemic brain and systemic injury may occur.[3] The seizures compromise cerebral vascular autoregulation, which in turn compromises hypothalamic autonomic regulation, and raised intracranial pressure may supervene. Complications such as cardiovascular collapse, arrhythmias, aspiration pneumonia, acute lung injury, and pulmonary hypertension may compromise cerebral oxygen delivery further. Metabolic derangement and cerebral and systemic acidosis with hyperpyrexia, rhabdomyolysis, and disseminated intravascular coagulation may cause multiple organ failure. Revealed seizures are then unusual.

Drug treatment divides into four stages[2]: that of premonitory, early, established, or refractory status epilepticus. Parenteral dosing with diazepam, lorazepam, or midazolam is preferred at the premonitory stage. Lorazepam is often preferred as it has a long duration of anticonvulsive effect and the best parenchymal distribution. Adverse events include a risk of respiratory arrest, hypotension, and impaired consciousness.[1]

Early management should include a prompt decision to use a long term parenteral anticonvulsant. Most patients in status epilepticus or who require a longer term anticonvulsant after acute presentation are treated with phenytoin. The pharmacology of phenytoin is complex but well understood. Given adequate

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