BMJ Group Improving Health Awards In association with MDDUS

Research paper of the year: interventions to improve health

Trish Groves introduces the shortlist for 2012


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This year's judges of the research paper of the year award have a tricky task, having to choose between four randomised trials based in very different communities. Which study will the judges feel has the greatest potential to improve health and healthcare; to help doctors make better decisions about clinical practice, public health, research methodology, or health policy; and to improve health outcomes for patients or populations?

Does training for traditional birth attendants reduce neonatal mortality in rural Zambia?

Neonatal deaths account for more than 40% of deaths in children aged under 5 worldwide, with about 75% occurring in the first week of life, and we're still some way from achieving the millennium development goal to reduce childhood mortality of two thirds by 2015. Christopher Gill (1) and colleagues conducted a cluster randomised trial with traditional birth attendants in a Zambian province that had rural health centres but no resident doctors and no hospital.[1] Among nearly 3500 home deliveries, mortality at 28 days was 45% lower among liveborn infants delivered by attendants in districts randomised to the intervention. The intervention comprised training in low tech resuscitation techniques such as drying and swaddling to avoid hypothermia, suction of the mouth and nose, and providing positive pressure ventilation with a reusable resuscitator mask when necessary; plus a single dose of amoxicillin and referral to a health centre for babies who became unwell over the next week.

Which short courses of combined treatment for visceral leishmaniasis in Bihar, India, are as good as standard treatment with amphotericin B and may head off the risk of resistance?

The randomised controlled trial by Shyam Sundar (2) and colleagues tackled visceral leishmaniasis (kala-azar), a major public health problem in many parts of the world. Treatment with liposomal amphotericin B can cure more than 95% of patients, but there's an imminent threat of resistance to it. In this trial more than 600 patients aged 5-60 with non-severe infection in Bihar, India, were randomised to treatment with amphotericin B infusion on alternate days for 30 days, or to one of three drug combinations given over no more than 10 days.[2] Patients fared well in all arms of the trial, with definitive cure rates at six months ranging from 93% to 98·7%, and with few harms.

Can a peer-led community based cardiovascular health promotion programme reduce hospital admissions for cardiovascular events among older people?

The rapid rise in non-communicable diseases in low and middle income countries makes the next shortlisted study potentially relevant around the world, even though it was set in Canada. In Janusz Kaczorowski and colleagues' (3) cluster randomised controlled trial, mid-sized Ontario communities were randomly allocated to receive either the Cardiovascular Health Awareness Program (CHAP) or no intervention.[3] Nearly 16 000 people aged over 65 in CHAP communities attended cardiovascular risk assessment and education sessions run by nearly 600 volunteers in community based pharmacies over a 10 week period. Automated blood pressure readings and self reported risk factor data were collected and shared with patients and their family physicians and pharmacists. After adjustment for hospital admission rates in the year before the intervention, CHAP was associated with a 9% relative reduction in the rate of hospital admissions for acute myocardial infarction, stroke, and congestive heart failure, equating to 3.02 fewer annual hospital admissions for cardiovascular disease per 1000 people aged 65 and over. For a whole population this community led intervention could have important public health implications.

For children with infection and advanced shock in sub-Saharan Africa, does bolus fluid resuscitation with either albumin or saline reduce mortality at 48 hours?

Malaria, sepsis, and other severe infectious conditions in children in sub-Saharan Africa are associated with high early mortality, often from hypovolaemic shock. The World Health Organization recommends fluid resuscitation only for children with advanced shock in such settings, but might not earlier use of fluids save lives? In the Fluid Expansion as Supportive Therapy (FEAST) study—Kathryn Maitland (4) and colleagues' stratified randomised controlled trial in Kenya, Tanzania, and Uganda—critically ill babies and children aged up to 12 with severe febrile illness were randomised to various regimens of immediate fluid resuscitation, while all of them also got appropriate antimicrobial treatment, intravenous maintenance fluids, and supportive care.[4] Children with severe febrile illness and impaired perfusion had boluses of intravenous albumin solution, 0.9% saline solution, or no bolus, while those who also had severe hypotension were randomly assigned to one of the bolus groups. The trial was stopped early, as soon as it became clear that giving fluid boluses (in all the intervention groups) significantly increased 48 hour mortality. The authors suggest that rapid reversal of the natural vasoconstrictor response may have been to blame, or perhaps reperfusion injury. Either way, if these interventions had been introduced widely without evaluation in a trial, it might have taken much longer for their risks to become clear.

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References are in the version on bmj.com.

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How the search for new drugs for neglected diseases is paying off

Academia, industry, and non-profit bodies are partnering to find new ways of treating neglected diseases, **Janice Hopkins Tanne** reports

The list of neglected diseases is long. Besides malaria, leishmaniasis, trypanosomiasis, and tuberculosis, there are dozens of other protozoan, viral, fungal, bacterial, helminth, and ectoparasite infections. These diseases affect 1.4 billion of the world's poorest people, who often live in remote, unstable areas.

But the list of new drugs is short. Between 1975 and 1999, only 16 of 1393 newly marketed drugs were for tropical diseases, said Curtis Chong, a haematology and oncology fellow at Dana Farber and Brigham and Women's Hospital in Boston, speaking at the annual conference on neglected diseases last month in Philadelphia, USA.

A better way is needed: repositioning old drugs for new purposes, discovering new drugs to treat neglected diseases, and developing new vaccines to prevent them. The buzzword is product development partnerships, whereby drug companies work with non-profit organisations and others in drug discovery endeavours.

Not-for-profit organisations and academia are filling the gap between research and industry's expertise in drug manufacturing and distribution, says Jean-Pierre Paccaud, director of business development at the Drugs for Neglected Diseases Initiative, a non-profit organisation working to develop new treatments for neglected diseases. Philanthropic and public funds can absorb the costs and risks of drug development. Industry can pick up the projects and market and distribute them.

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Already 17 drugs, vaccines, and diagnostics have been developed through partnerships between non-profit organisations and the drug industry. Paccaud named as examples ASAQ, a fixed-dose artesunate combination for malaria developed by the neglected drug initiative that Sanofi manufactures, registers, and distributes in more than 25 African countries; fexinidazole for African sleeping sickness, also developed as a collaboration between the neglected diseases initiative and Sanofi, which is now entering phase II trials; dispersible artemether and lumefantrine (Coartem), a paediatric antimalarial combination developed by the Medicines for Malaria Venture, which Novartis manufactures, registers, and distributes; and meningitis vaccine (MenAfriVac) developed under the supervision of the Meningitis Vaccine Project, which the Serum Institute of India manufactures and WHO distributes.

Commercial partnerships

Ian Gilbert, head of chemistry at the drug discovery unit at the University of Dundee, says: "Drug discovery is hugely expensive. There's no commercial market [for drugs against many neglected diseases]. Pharmaceutical companies are contributing a lot but they need help in understanding the biology. Academic labs are helping, as are the not-for-profit organisations. At Dundee we have both the basic biological understanding of parasitic diseases and have developed drug discovery programmes against a number of them."

Jacqueline Fine, associate director for global outlicensing and asset management at Merck Research Laboratories, told the conference that partnerships were essential. She said Merck had partnered with the Wellcome Trust to establish a joint venture, the MSD Wellcome Trust Hilleman Laboratories, that operates like a biotech company but with a not-for-profit operating model to meet the vaccine needs of low income countries.

James Brown of GlaxoSmithKline said there was a critical need for new classes of drugs because resistance to existing drugs was widespread.

GSK uses teams to find new drugs for malaria, tuberculosis, and other neglected diseases by concentrating on novel targets that affect the pathogen directly as well as potential interactions between host and pathogen. Scientists in the company's diseases of the developing world unit in Tres Cantos, Spain, have access both to the firm's internal research and development resources and to external collaborations. The unit fosters alliances with other institutions, funding agencies, and visiting researchers.

Brown said that the GSK unit had screened about two million compounds for possible action against *Plasmodium falciparum*, the most dangerous form of malaria. All the data have been published and are accessible on the web.

Repurposing

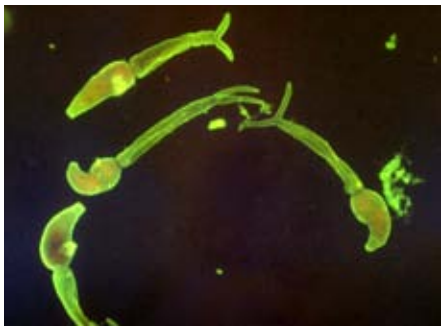
Existing drugs show new promise when they are repurposed to treat neglected diseases. Aris Persidis, president of Biovista, said that the company's Clinical Outcomes Search Space used experimental data from many sources to create a multidimensional barcode of characteristics for given drugs. The code is compared with the barcodes for other drugs and the disease. Barcodes that are similar suggest that the drug's mode of action correlates with the disease of interest.

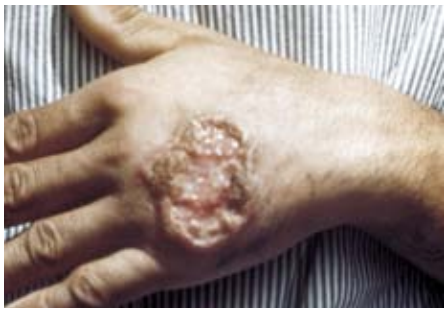
Chong proposed screening drug libraries based on hits of known clinical properties, thus shortening the time from animal testing to testing in humans. He said registries suggest there are about 9500 drugs used in the world. He described several libraries of compounds, among them the Johns Hopkins clinical compound screening initiative, which will build a library of every drug approved by the Food and Drug Administration or that has passed through phase II clinical trials and make them available in a format for screening. The drugs can be screened for any clinical target through collaborative agreements. Because the toxicity and pharmacokinetics are known, promising drugs can be quickly moved into clinical trials.

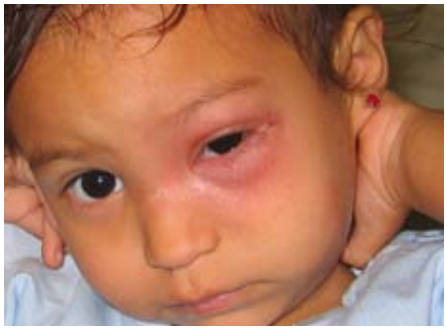
One promising drug already identified against malaria is astemizole, a non-sedating antihistamine that was withdrawn in the US but is available in 30 countries, both by prescription and over the counter, including in malaria endemic countries.

Leishmaniasis

Two speakers described new approaches to leishmaniasis. This bloodborne pathogen is transmitted by sand flies. Visceral leishmaniasis kills more people than any parasitic disease except malaria, said Hira Nakhasi, director of emerging







Clockwise from top l: the parasite that causes schistosomiasis; community drug distributor during an onchocerciasis treatment campaign in Cameroon; tsetse flies, which transmits trypanosomiasis; schoolboys in Ghana receive mosquito nets; a young patient with Chagas in El Salvador; Leishmaniasis patient with skin ulcer in Central America

PHOTOS: WHO AND CDC

and transfusion related diseases at the FDA.

US civilians and military staff travelling to endemic areas are at risk of Leishmania infection. In addition, asymptomatic immigrants from endemic areas could transmit the disease by blood donation. There are no screening assays or vaccines. The Leishmania parasite tends to develop resistance against the available drugs. The sand fly vector for Leishmania is present in the southern US. With global warming, the disease may spread further to southern and coastal regions of the United States.

A vaccine using live attenuated parasites may be possible, Nakhasi said. Live attenuated parasites protect against virulent challenge in animal models. They are safe as a vaccine because they do not revert to the wild type in the animal model and do not survive in sand flies. Nakhasi said he was looking for partnerships to develop the vaccine further.

Susan Wyllie of the University of Dundee suggested repurposing fexinidazole as oral therapy for visceral leishmaniasis. Phase I trials for fexinidazole to treat human African trypanosomiasis have already been completed so it might be possible to fast track the drug to phase II trials for leishmaniasis. Phase II and III trials for trypanosomiasis are scheduled for mid-2012.

Paccaud said the past decade had seen promising changes in developing drugs for neglected tropical diseases. He pointed to product development partnerships and the January 2012 London Declaration on Neglected Tropical Diseases. In the declaration, major pharmaceutical companies, international foundations, the US Agency for International Development, and the World Bank came together to sustain, support, and extend programmes that ensure the supply of treatments for many neglected diseases, increase research and development, provide technical support to endemic countries, and provide updates on progress in reaching WHO's 2020 roadmap for neglected tropical diseases.

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