Do we need new drugs against human African trypanosomiasis?


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Human African trypanosomiasis (sleeping sickness) is caused by the parasite *Trypanosoma brucei* and is fatal if untreated. According to WHO reports, three epidemics have occurred: the first between 1896 and 1906, the second in the 1920s, and the third in the 1970s. The official numbers of new cases of human African trypanosomiasis have decreased to less than 10 000 a year in recent years.[1,2] However, the disease can strike back aggressively, as has been shown repeatedly in Sudan.[3]

Available drugs are at least 30 years old and have severe drawbacks. Those used for the first stage of the disease are less toxic and easier to give than those for the second stage, but available drugs produce dangerous adverse effects and are often effective against only one of the two stages or only the chronic form (caused by *T b gambiense*) or the acute form (caused by *T b rhodesiense*) of disease (table).

Introduction of nifurtimox–eflornithine combination treatment (NECT) in 2009 was an enormous step forward,[5] reducing the duration of treatment with parenteral eflornithine to 1 week down from at least 14 days with eflornithine alone. NECT, a reformulation of existing drugs, is the first new treatment for human African trypanosomiasis in more than 25 years. It has not been approved in any country, but was added to the WHO list of essential medicines in 2009.[2,6] However, NECT is expensive.

Some other drugs are in clinical trials.[7] The sulfone and sulfoxide metabolites of fexinidazole are effective in animal models of the disease. Fexinidazole is bioavailable orally, can cross the blood–brain barrier, and is effective in advanced stages of *T b rhodesiense* and *T b gambiense* disease. The benzoxaborole SCYX-7158 has satisfactory potency against *T b rhodesiense* and *T b gambiense,* and has good pharmacokinetic properties in vitro and after oral administration in rodents and non-human primates. It can cross the blood–brain barrier and is metabolically stable, making it feasible to treat both disease stages. The pentamidine analogue pafuramidine was being tested in phase 3 clinical trials as an oral drug for first-stage human African trypanosomiasis, but these trials were stopped because of the drug's nephrotoxicity. Finally, melarsoprol complexed with either hydroxypropyl-β-cyclodextrin or methylated β-cyclodextrin for solubility enhancement is in clinical trials.[8]

The presence of at least two potential new candidate drugs in the pipeline is an impressive achievement compared with the situation 10 years ago, but this is still not enough given that none of these drugs is in phase 3 trials and that up to 90% of drug candidates, like parfuramidine, do not make it to market.

This drug pipeline for human African trypanosomiasis should not be allowed to run dry. More than a century ago, Paul Ehrlich was among the first people to recognise that science and health systems ought to do their utmost to combat this devastating disease. At Ehrlich´s time, the combination of organic arsenicals almost resulted in the eradication of the disease, but only with a great effort from the public health and government systems.[7] Unfortunately, the prevalence of the disease is higher now than it was in the beginning of the 20th century.

In view of this weak supply of new candidate drugs from drug companies, alternative approaches are needed. Can academia and private-public partnerships provide enough resources for drug discovery and development? Can the academic research community communicate with health workers in the field to redefine the needs and necessities for an ideal human African trypanosomiasis

	Discovery date	Disease stage; *Trypanosoma brucei* subspecies	Administration route	Adverse effect
Suramine	1922	Stage one; *T b rhodesiense*	Intravenous	Nephrotoxicity, allergic reactions
Pentamidine	1941	Stage one; *T b gambiense*	Intramuscular	Hypotension, glucose imbalances
Melarsoprol	1949	Both stages; *T b rhodesiense*	Intravenous	Painful injection, reactive encephalopathy, increasing number of treatment failures mostly because of toxicity
Nifurtimox	1967	Both stages; both subspecies	Oral	Gastrointestinal symptoms, neuropathies
Eflornithine	1981	Stage two; *T b gambiense*	Intravenous infusion	Reversible haematological abnormalities, diarrhoea, hair loss
Nifurtimox-eflornithine	2009	Stage two; *T b gambiense*	intravenous (eflornithine), oral (nifurtimox)	Gastrointestinal symptoms, headache, musculoskeletal, vertigo

Table: **Available drugs for human African trypanosomiasis[4]**

drug and focus their efforts accordingly? And if such communication would be possible, would this spur drug companies and local governments into action.

Neglected tropical diseases, including human African trypanosomiasis, need more attention. Solutions will probably come from unconventional approaches. The combined efforts of academia and the pharmaceutical industry might help to decrease the suffering of people affected by human African trypanosomiasis, and could lead to fair distribution and provision of health care.

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We declare that we have no conflicts of interest. We thank the German Research Centre Foundation for financing our work at the Collaborative Research Centre SFB630.

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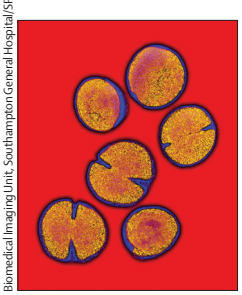
Community-associated MRSA from the Indian subcontinent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The emergence and global dissemination of multidrug-resistant Gram-negative bacteria from the Indian subcontinent has received much attention. Less attention, however, has been given to reports describing the emergence in the past 5 years of two community-associated meticillin-resistant *Staphylococcus aureus* (MRSA) lineages from the Indian subcontinent—sequence types (ST)772 and ST22. Both lineages express Panton-Valentine leucocidin (PVL), which is associated with skin and soft tissue infections. ST772 and ST22 MRSA expressing PVL have become increasingly prevalent in India and have caused outbreaks and infections elsewhere in the world, which are often epidemiologically linked to India.[1–3] Findings from a whole-genome sequencing study have shown that, within the ST22 population, PVL-producing ST22 strains are distinct from the well known nosocomial UK EMRSA-15 clone.[4] Thus earlier studies using pulsed-field gel electrophoresis and multilocus sequence typing most likely incorrectly assigned PVL-producing ST22 strains as UK EMRSA-15-like. [5] Early reports of PVL-positive ST22 strains were of meticillin-susceptible *S aureus*.[6] Reports from India indicate that PVL-producing ST22 MRSA strains are now common in hospitals and the community.[6–8] Outbreaks outside of India have been reported in England,[9] Germany,[10] Japan,[2] and Australia.[3] In 2010, ST22 PVL-producing MRSA was the most common multiresistant PVL-producing MRSA strain in England.[11] Of concern is that ST222 strains that produce PVL are typically resistant to ciprofloxacin, erythromycin, gentamicin, and trimethoprim—a degree of multidrug-resistance rarely seen in community-associated MRSA. Strains from this lineage often cause recurrent abscesses, have proven difficult to eradicate,[2] and have enhanced biofilm formation compared with other *S aureus* strains,[2] and health-care staff have been implicated as vectors in nosocomial outbreaks.[1,9]

ST772 meticillin-susceptible *S aureus* was first described in Bangladesh[12] and in India in 2004.[6] ST22 and ST772 PVL-producing MRSA strains are now replacing ST239 MRSA as the predominant lineage in Indian hospitals.[7,8,13,14] The infiltration and displacement of endemic hospital-acquired and community-associated MRSA in health-care settings in India echoes the experience seen with other community-associated MRSA strains in other countries such as the USA300 strain in North America. ST772 PVL-producing MRSA has caused an outbreak in Ireland,[1] and in England the number of cases rose from ten in 2007 to 61 in 2009, and by 2010 was one of the most common multidrug-resistant PVL-positive MRSA lineages in England.[11]

As with Gram-negative bacteria in the Indian subcontinent, the widespread use of antibiotics, poor public