Recent advances in tropical medicine

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Summary
There have been significant advances in both the classical and neglected tropical diseases, with Guinea worm looking set to be the next disease after smallpox to be eradicated. Aided by a combination of enhanced understanding of the biology of the pathogens, intensification of immunisation activities or mass drug administration, together with the development of synergies with control programmes for co-endemic tropical diseases, polio, lymphatic filariasis, trachoma and onchocerciasis all appear to be in global decline, with good prospects for eventual successful elimination. While the global incidence of new cases of leprosy continues to decrease, the focus of leprosy control efforts has shifted following more widespread recognition that cure of infection does not necessarily prevent disability. Expansion in funding for HIV/AIDS and malaria provides some grounds for optimism about the control of these diseases. However, ongoing education and access remain essential to increasing the uptake of HIV testing and decreasing transmission. Meanwhile, the rise of drug-resistant tuberculosis and malaria is concerning, and the emergence of the highly pathogenic avian influenza A and re-emergence of viruses such as chikungunya and West Nile virus, without significant recent progress in vaccine development, pose additional ongoing challenges to tropical medicine physicians worldwide.

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1. Malaria

1.1. Drug resistance

Clinical resistance has arisen to all classes of antimalarials used to date, barring the artemisinin derivatives. Chloroquine resistance is now virtually universal in Plasmodium falciparum and the efficacy of sulfadoxine-pyrimethamine (Fansidar) has become increasingly compromised. Monotherapy and widespread, indiscriminate use of antimalarials have encouraged the selection of drug-resistant strains. Encouragingly, chloroquine-sensitive P. falciparum has re-emerged in Malawi 13 years after chloroquine was
abandoned, but the clinical application of this observation has yet to be realised.\(^1\) Whether the complete eradication of malaria is a realistic goal remains to be seen.\(^2\)

### 1.2. Antimalarial combinations

To maximise the effectiveness of treatment and to delay the development of resistance to newer drugs, treatment with combinations of antimalarial drugs is now recommended.\(^3\) Artemisinin derivatives rapidly clear malaria parasites from the blood and combinations including these drugs (e.g. artemisinin with amodiaquine or mefloquine, and artemether with lumefantrine) have been strongly endorsed by WHO since 2001.\(^4\) Non-artemisinin-containing combinations (e.g. sulfadoxine-pyrimethamine with amodiaquine) are advised only if artemisinin-based combination therapy (ACT) is unavailable or unaffordable.

Affordability remains an issue, as ACTs are nearly 10 times as expensive as previous first-line choices. Despite this, since 2001, 41 of 54 African countries in which malaria is endemic have changed their malaria treatment protocols to make ACTs first-line. The impact of these changes on morbidity and mortality has yet to be documented. Whilst data exist to support the preferential use of artemisinin over quinine for the initial treatment of severe malaria in adults, the results of an equivalence study in African children are awaited.\(^5\)

### 1.3. Control

An international commitment to halve the burden of malaria by 2015 has been supported by considerable increases in funding for malaria control. Recent analysis, however, suggests that for the 1.4 billion people exposed to stable \(P. \)falciparum malaria risk there is an annual budget of US$1 billion dedicated for control — less than US$1 per person at risk per year.\(^6\)

### 1.4. Knowlesi malaria

Malaria in humans due to a fifth malarial species, \(P. \)knowlesi, has now been well documented in Malaysian Borneo and Peninsular Malaysia. Recent evidence indicates that it may be more widespread even than this. Often misdiagnosed as \(P. malariae, P. \)knowlesi is capable of causing severe disease and even death.\(^7,8\)

### 2. Tuberculosis

#### 2.1. Diagnosis

Owing to the insensitivity of direct microscopy of clinical samples and the widespread unavailability, imperfect sensitivity and long lag-time of mycobacterial culture, the diagnosis of tuberculosis (TB) continues to be based on clinical presentation and the Mantoux test, a semi-quantitative test that has remained essentially unchanged since its development 100 years ago. Both positive and negative Mantoux results must be interpreted with caution. There is an urgent need for the development of improved diagnostic tests (based, for example, on the detection of \(\gamma\)-interferon release by peripheral blood T-cells) in formats that can be practically and economically deployed in resource-poor settings.\(^9,10\)

#### 2.2. Control

After increasing through the 1990s and early 2000s as a result of the HIV pandemic and the break-up of the Soviet Union, amongst other factors, the per capita global incidence of TB now appears to be in decline. In 2005 there were an estimated 8.8 million new cases and 1.6 million deaths.\(^11\) In 2006 the WHO launched the Stop Tuberculosis Strategy, a six-point plan aiming to reduce TB prevalence and mortality to less than 50% of 1990 levels by 2015.\(^12\) It is currently too early to assess the global impact of this strategy, but pilot studies in Thailand suggest that it may enhance case-finding (including in the private sector) and help patients diagnosed with TB engage with HIV services.\(^13\)

#### 2.3. MDR- and XDR-TB

Multidrug-resistant TB (MDR-TB) is caused by \textit{Mycobacterium tuberculosis} resistant to both rifampicin and isoniazid; extensively drug-resistant TB (XDR-TB) is resistant to isoniazid, rifampicin and fluoroquinolones and either aminoglycosides or capreomycin or both. Such strains have emerged because of inadequate treatment regimens and poor compliance, and pose a serious threat to TB control worldwide. WHO estimates that in 2004, 4.3% of all cases of TB were due to MDR-TB.\(^14\)

XDR-TB has now been identified in more than 40 countries. Relatively few laboratories are able to test the susceptibility of \(M. \)tuberculosis isolates to second-line drugs, so population-based data are generally lacking. Improved diagnostic facilities and expanded access to second- and third-line drugs are needed, since XDR-TB is associated with extremely high mortality.\(^15\)

### 3. HIV/AIDS

The annual HIV/AIDS estimates released by UNAIDS suggest that in 2007 there were 33.2 million individuals living with HIV, of whom 15.4 million were women and 2.5 million were children aged less than 15 years.\(^16\) The 2007 total global prevalence figure is 16% less than the corresponding estimate for 2006, a decrease that is primarily attributed to improvements in the mathematical models used to calculate the likely prevalence in India and sub-Saharan Africa. Although UNAIDS has been criticised for the way in which it calculates and interprets its estimates,\(^17,18\) it is encouraging that current data suggest that prevalence is beginning to plateau.

Access to and uptake of HIV testing remain major barriers to control. In sub-Saharan Africa fewer than 10% of those infected with HIV know they are infected.\(^19\) The availability of antiretroviral drugs to those in developing countries is also problematic; although treatment coverage was declared a global health emergency in 2003, WHO’s commitment to increase antiretroviral treatment coverage from 300,000 to 3 million people in low- and middle-income countries by

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the end of 2005 (the ‘3 by 5’ target) was not fulfilled. By December 2005 approximately 1.3 million people in low- and middle-income countries were receiving antiretrovirals.

4. Emerging and re-emerging diseases

4.1. Avian influenza

Highly pathogenic avian influenza A (H5N1) virus emerged in Southeast Asia in late 2003, causing disease in birds and then in humans. By January 2008 there had been 352 human cases in 14 countries, resulting in 219 deaths.20 Most people infected had been in close contact with poultry, but in September 2004 the first reasonably conclusive cases of person-to-person transmission were reported between members of a family living in Thailand.21 The virus is not yet pandemic, mainly because current strains are not efficient at person-to-person spread.22 Vaccines are in development.

International guidelines for the pharmacological management of H5N1 were published in January 2007, recommending oseltamivir for treatment of confirmed cases and oseltamivir or zanamivir as chemoprophylaxis in household or close family contacts.23 The quality of direct evidence supporting these recommendations is acknowledged to be low.

4.2. Chikungunya

Chikungunya (‘that which bends up’ — referring to the crippling arthralgia that infection may produce) is a disease caused by an alphavirus transmitted by Aedes spp. mosquitoes. The first recorded epidemic was in Tanzania in 1952–3. Severe polyarthralgia, fever and a maculopapular rash are the most prominent clinical features. Treatment is supportive; vaccine trials are in progress.

In March 2005 a chikungunya epidemic began on the Indian Ocean island of Reunion. More than 266 000 people were infected, peaking in February 2006.24 The virus spread to India, causing more than 1.3 million cases,25 and from there to Italy, resulting in 205 cases by September 2007.26

4.3. West Nile virus

First isolated in Uganda in 1937, West Nile virus is a flavivirus that has long caused sporadic outbreaks of a febrile illness in Africa, the Mediterranean and eastern Europe.27 In humans, West Nile virus may also result in neuroinvasive disease (meningitis, encephalitis or acute flaccid paralysis). The virus emerged in the Americas for the first time in New York City in 1999 and subsequently spread in the USA, causing major declines in several North American bird species and seasonal epidemics in humans. During this outbreak a newly dominant genotype (WN02) emerged that has a significantly shorter incubation period in the vector, culicine mosquitoes.28 From January to November 2007, 3304 cases were reported to the Centers for Disease Control (CDC) from 43 states in the USA; 93 were fatal.29

5. Polio

In 1988 polio was scheduled for global eradication by the year 2000.30 As a result of intensive international efforts the annual number of cases worldwide declined from an estimated 350 000 in 1998 to 719 in 2000, an encouraging decrease of 99.7%.31 Completing the process of eradication has proved difficult, however. In Nigeria, immunisation activities were suspended in 2003 and 2004 because of rumours that vaccines were adulterated with anti-fertility drugs or HIV.32 This interruption in control efforts has led to outbreaks as far afield as Indonesia, Botswana and Saudi Arabia. Other challenges to the global eradication campaign include political instability, conflict, fatigue in communities and vaccination teams, difficulties in sustaining surveillance in remote and underprovided communities, and an increasing awareness of vaccine-associated paralytic poliomyelitis (VAPP) in 2–4 vaccinees per million.33,34

In January 2008 poliovirus was still considered endemic in four countries (Pakistan, Afghanistan, India and Nigeria), while another five countries had active transmission of imported virus; a total of 1083 cases due to wild virus were confirmed during 2007.31 For the last 7 years the annual number of cases has ranged between 483 (in 2001) and 1997 (in 2006). In response, an integrated global network for molecular surveillance of each wild virus isolate has been constructed to monitor progress, understand local and international transmission pathways, and propose appropriate control strategies. In some conflict areas it has been possible to suspend hostilities to permit national immunisation days to proceed.33

6. Leprosy

Unlike polio, for which eradication was set for 2000, leprosy was scheduled for global ‘elimination as a public health problem’ by the same year — defined as the reduction in prevalence to less than one case per 10 000 persons, based on the hypothesis that at this prevalence or lower, transmission would be interrupted. This target raised the profile of leprosy as a disease and galvanised control efforts. Unfortunately, determining leprosy elimination using prevalence as the criterion is problematic; the disease may have an incubation period of up to 20 years and certifying successful elimination, as the WHO did in May 2001, led to reduction in both clinical service provision and funding for leprosy research.35,36

The campaign approach has now been discontinued and the ongoing focus is the timely detection of new cases, early treatment with effective chemotherapy, prevention of disability and provision of rehabilitation. Case detection (rather than prevalence) will be the main indicator used to monitor progress. In 2006, 259 017 new cases of leprosy were registered worldwide, a decrease of 13% compared with 2005, continuing a steady decline that has been sustained during the current decade.37 Only four countries of the 122 that were leprosy-endemic in 1985 had a registered prevalence of leprosy of more than one case per 10 000 population: Brazil, the Democratic Republic of Congo, Mozambique and Nepal.37 The prospects for maintaining progress against leprosy seem good; humans are the main...
reservoir of infection, free multidrug therapy has been available since 2000 and drug-resistant strains of *Mycobacterium leprae* have not yet proven problematic.

7. Schistosomiasis

The Schistosomiasis Control Initiative (SCI) has made considerable progress in the control of this infection in Africa. By mid 2008 approximately 40 million treatments had been administered in six countries, reaching over 20 million individuals, although approximately 10 times this number of people are thought to need treatment. In every case praziquantel has been co-administered with the anthelmintic albendazole, but from 2007 onwards the emphasis changed and a 'rapid impact' package of up to four drugs is now offered, as appropriate, so that schistosomiasis, intestinal helminths, trachoma, lymphatic filariasis and onchocerciasis can be controlled in an integrated attack on neglected tropical diseases (NTDs). The aim is to bring donated drugs to the poorest populations of sub-Saharan Africa at an estimated cost of 25 pence per person annually.

8. Blindness due to trachoma and onchocerciasis

In 2002, trachoma and onchocerciasis accounted for about 3.6% and 0.8% of the total global burden of blindness, respectively. Both are programmed for elimination by 2020 as part of the WHO-supported global initiative, VISION 2020: the Right to Sight. Significant progress has been made in controlling both diseases.

Trachoma, caused by ocular strains of *Chlamydia trachomatis*, is endemic in over 50 countries and leads to irreversible blindness. Prevention is based on the 'SAFE' strategy, which involves: Surgery for advanced disease, Antibiotics to clear infection, Facial cleanliness and Environmental improvement to reduce transmission. In 2006, Morocco became the first country to eliminate trachoma using this strategy; Ghana, Mauritania, Nepal and Vietnam are on track to achieve elimination by 2010.

Onchocerciasis, or river blindness, due to infection with the nematode *Onchocerca volvulus*, is transmitted through the bite of the blackfly, *Simulium*. By spraying larvicides from aircraft over blackfly breeding sites and by population-based distribution of the microfilaricide ivermectin, the Onchocerciasis Control Program (OCP) (1974–2002) achieved cessation of transmission in nearly all areas of 10 of the 11 West African countries in which it operated. The African OCP, launched in 1995, currently protects 40 million people in 19 countries through community-directed ivermectin distribution. The latter programme is scheduled to close in 2010; there has been a recent call for it to extend its working life to at least 2015 and enlarge its activities to include pockets of residual disease activity in former OCP countries.

Alarming, there is some recent evidence from Ghana of a reduction in ivermectin’s ability to block the release of intrauterine microfilariae by adult female worms although, oddly, the microfilaricidal action of the drug appears undiminished. New tools such as anthelmintic vaccines, a safe macrofilaricide or chemotherapy targeted against *Wolbachia* (a bacterial endosymbiont of *O. volvulus*), may be required. 

9. Lymphatic filariasis

Lymphatic filariasis affects more than 120 million people, of whom over 40 million are debilitated or disfigured by the disease. It is caused by infection with the nematode worms *Wuchereria bancrofti*, *Brugia malayi* or *B. timori*, the microfilariae of which are spread by a variety of mosquito vector species in defined geographical areas. The main aims of the Global Programme to Eliminate Lymphatic Filariasis (GPELF) are to interrupt transmission of infection and to alleviate suffering and disability produced by the disease in the 83 countries in which it is endemic.

Mass drug administration (MDA) to reduce transmission (and therefore morbidity) is conducted through the annual distribution of single doses of two microfilaricidal drugs for at least 5 years: diethylcarbamazine plus albendazole, or ivermectin plus albendazole in areas in which onchocerciasis is co-endemic. Since the initiation of GPELF in 2000 there has been a rapid expansion in MDA programmes, from 12 countries covering 3 million people in 2000, to 44 countries covering 258 million people by the end of 2006. These efforts have produced significant gains. In Egypt, studies in sentinel villages suggest that five rounds of MDA with >80% coverage may have been sufficient to eliminate the infection in most endemic localities in the country.

A possible alternative or adjunctive approach to MDA, as with onchocerciasis, is to administer antibiotics active against *Wolbachia*, essential bacterial endosymbionts of adult filariae. This approach has gained some support from recent randomised controlled trial data.

10. Dracunculiasis (Guinea worm)

Nine countries, all in sub-Saharan Africa, are still considered to have endemic dracunculiasis. The number of cases reported dropped from 892,055 in 1989 to 10,674 in 2005 and rose again to 25,217 in 2006, probably because of better reporting from the eradication programme in Sudan. Ministers of health from the remaining endemic countries have declared their commitment to global eradication of dracunculiasis by 2009. Considerable effort will be required to achieve this goal, particularly in Ghana and Sudan. However, there are no technical constraints to eradication. Contracted by drinking water containing copepods infected with larval *Dracunculus medinensis*, the disease could be eradicated in the remaining 4086 endemic villages by the provision of safe water supplies such as boreholes, education of the community about not swimming or wading in sources of drinking water, and universal filtering of drinking water through finely woven cloth.

11. Conclusions

Guinea worm looks set to be the next disease after smallpox to be eradicated. Aided by a combination of enhanced understanding of the biology of the pathogens, intensification of immunisation activities or mass drug administration,
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and the development of synergies with control programmes for co-endemic tropical diseases, polio, lymphatic filariasis, trachoma and onchocerciasis all appear to be in global decline, with good prospects for eventual elimination. While the global incidence of new cases of leprosy also continues to decrease, the focus of leprosy control efforts has shifted following more widespread recognition that cure of infection does not prevent disability in the affected individual. Expansion in funding for HIV/AIDS and malaria provides some grounds for optimism for the control of these diseases. Meanwhile, the rise of drug-resistant TB and emerging and re-emerging viruses pose additional ongoing challenges to tropical medicine physicians worldwide.

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