established best practice.[6–7] It departs from previously suggested phrasing that the research should be of "direct benefit to persons with that particular condition," which would have precluded much observational or epidemiological research. One residual point is that the new bill restricts research to that which examines the causes or treatment of "a condition attributable to the impairment [or disturbance] of the mind or brain." This may preclude research in intensive care units where the subject is incompetent not due to neurological disease, but instead due to sedative therapy which is essential to their care. One solution would be to recognise that essential therapy is part of the overall burden of disease, and permit research into the underlying illness when such therapy compromises competence. It is also important that the mental capacity bill is interpreted to recognise explicitly that it is ethical to proceed when clinical equipoise exists. Clear and enabling guidance notes, or appropriate amendments, are therefore necessary.

Some ground has also been achieved in the human tissue bill since an earlier draft of this editorial was shared with Department of Health officials. New amendments have just been announced that allow the secretary of state to specify conditions under which consent can be presumed for research involving tissue from an incompetent person.[8] These conditions have not been itemised. It is to be hoped they will interact simply and clearly with the conditions in the revised mental capacity bill. The secretary will also be given power to set conditions allowing analysis of an incompetent person's DNA. This should alleviate the problem in earlier versions of the human tissue bill which, ignoring the Human Genetics Commission's 2002 recommendation,[9] did not allow DNA to be analysed for the benefit of a family member (for example, to predict the risk of breast cancer). These improvements to the human tissue bill will not be realised until regulations are drafted and approved by parliament. It will be important to ensure they are prepared swiftly and that the details are sound.

The consequences of inadequate legislation in these areas are not trivial. Clear and strictly conditioned policies for non-therapeutic research and the practice of clinical genetics are essential if we are to improve care and outcome in these settings. Carefully drafted legislation, underpinned by sensible guidance, could facilitate research while addressing legitimate public concerns.

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Newer drug combinations for malaria

May be impractical unless diagnostic accuracy can be improved

Resistance of parasites to cheap, first line malaria drugs is a major obstacle to reducing the more than one million deaths due to malaria each year worldwide. Comparing the number of parasitologically confirmed cases of malaria with those that are presumptively diagnosed reveals shockingly high rates of overdiagnosis at peripheral and community levels where self treatment is routine.[1] If more expensive drug treatments are introduced, this degree of misdiagnosis of malaria cannot be condoned or sustained.

Misdiagnosis of malaria in poorer countries

In sub-Saharan Africa more than 80% of individuals with malaria self treat fevers with antimalarial drugs without seeking help from the formal health sector.[2] Sixty per cent of children with fever in Kenya, and 83% in Togo, were treated at home with a malaria drug.[3 4] Clinical signs alone are also used at primary healthcare facilities, which lack laboratories for malaria diagnosis. This approach is sensitive but not specific, so that in areas with intermittent malaria transmission it is common for three quarters of febrile patients to be advised to take antimalarials for a non-malarial illness. Attempts to improve clinical diagnosis by using simple algorithms have had only modest success.[5] A combination of fever, splenomegaly, and pallor of the nailbed—the best predictors for malaria parasitaemia in Malawi—had 41% specificity, compared with a specifity of 21% when fever alone was used.[6]

These high rates of misdiagnosis of malaria have been tolerated because first line antimalarials are relatively inexpensive and non-toxic. Misdiagnosis

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results in prolonged and worsening illness, reduced productivity and school attendance, unnecessary purchase of drugs and toxicity, and economic and opportunity costs of clinic visits. At the population level, overdiagnosis of malaria increases the perceived levels of drug resistance (fever is unresponsive to antimalarials) as well as real drug resistance (induced by exposure of the parasite to subtherapeutic concentrations of drugs).[5]

Higher drug costs should stimulate improvements in diagnosis

Resistance to chloroquine, which costs $0.08 US (£0.05; €0.07) per adult dose, is rapidly spreading throughout Africa, and it has been replaced in several countries in south eastern Africa by sulfadoxine-pyrimethamine, which costs $0.12.[7] Detection of resistance to sulfadoxine-pyrimethamine is currently driving recommendations for newer, more expensive, therapeutic strategies based on combinations of two antimalarials (including artemisinin derivatives). The rationale is that simultaneous use of two drugs with different modes of action will inhibit the development of resistance to either component. These combinations cost between $1.12 (sulfadoxine-pyrimethamine plus artesunate) and $3.90 (mefloquine plus artesunate) per adult dose.[8]

Microscopic examination of a blood smear is the gold standard method for the diagnosis of malaria. Difficulties in servicing microscopes, training and supervising technicians, and educating clinicians to use results appropriately mean that microscopy is not usually available at subdistrict facilities, where the burden of malaria is greatest.[9 10] Rapid diagnostic tests based on detection of malaria antigens are currently the only feasible option for the field diagnosis of malaria. These are dipsticks that provide a simple "present" or "absent" result, usually represented as a coloured line, on contact with blood and have been successfully used in Colombia, Thailand,[11] and Tanzania. Their widespread use is restricted by cost and their inability to differentiate clinically significant parasitaemia from the low level asymptomatic parasitaemia that is common in highly endemic areas.

Balancing the costs

Getting the balance right between investment in accurate diagnosis and the cost of new drug regimens will be influenced by the prevalence of malaria and patterns of resistance, technical and clinical skills, and available resources. These vary widely between and even within countries, making it difficult and inappropriate to develop uniform international drug policies for malaria.

Is it reasonable to expect governments to make rational decisions about investing in accurate diagnosis of malaria without information about the overt and hidden costs of incorrect diagnosis? To formulate appropriate strategies, policy makers need information on the cost effectiveness of various combinations of diagnostic tools and treatment regimens. Calculation of costs must not only include drugs and diagnostic tests, but also the knock on effects of improving diagnostic accuracy such as reductions in illness, death, and drug resistance. In countries where malaria is still susceptible to first line cheap drugs and the rate of misdiagnosis is low an investment in accurate diagnosis of malaria may be hard to justify. However, the diagnosis of malaria needs to be accurate in low transmission zones where rates of overdiagnosis are high, single agent treatments are failing, and more expensive combination regimens are being considered.

The way forward

With increasing resistance to malaria, many resource poor countries clearly will not be able to sustain the current level of malaria misdiagnosis. The international effort that is being put into developing new malaria drugs should be paralleled by a commitment to improve the availability of accurate diagnostic tools for malaria, so that drugs can be targeted to people with definite malarial illness. International agencies have a key role in providing the evidence that governments need to make these decisions and to get appropriate evidence based diagnostic strategies for malaria into practice.

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