COMMENTARY

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Improved rapid tests for malaria are needed to accurately diagnose infection and to avoid over-prescription of drugs.

Neglected tests for neglected patients

Alternative ways to develop diagnostic tools for use in resource-poor settings can, and do, exist, argue **Martine Usdin**, **Martine Guillerm** and **Pierre Chirac** of Doctors without Borders.

Organizations such as Doctors without Borders (Médecins Sans Frontières, or MSF) provide emergency medical assistance to populations that do not have access to medical care. In the various settings in which MSF works, the absence of suitable diagnostic tests is far more the rule than the exception. The need for reliable diagnostics is closely linked to the need for safe and effective treatments, and many of the diseases considered 'neglected' in terms of treatment are equally neglected in terms of diagnosis. In the case of sleeping sickness, for example, existing treatments are highly toxic and can kill up to 10% of patients[1]; an accurate diagnosis must therefore be made before starting treatment. In the case of malaria — which kills more than 1 million people a year[2] — misdiagnosis of the disease from clinical signs alone[3,4] is often a problem. The need to avoid overprescribing antimalarial drugs, to minimize costs and the risk of developing resistance, reinforces the need for an adequate diagnostic test.

MSF and other humanitarian organizations face similar challenges in diagnosing other major diseases in resource-poor settings, notably tuberculosis, HIV in infants and HIV-associated infections such as cryptococcal meningitis. The lack of suitable diagnostic tests for use in the field means that the identification of many diseases is based solely on clinical symptoms. The long list of diseases with no field-adapted diagnostic tools includes leishmaniasis, shigella, typhoid and bacterial meningitis. MSF is attempting to address these needs by exploring how available technology can best be used, either by improving existing tests or by developing new, field-adapted ones.

What is needed?

The reasons for the gaps between need and availability are manifold. In some cases, existing tests are not sensitive or specific enough, or some of the fundamental biology of the disease is still not known. In other cases, technologies do exist but are too complex, too expensive or not suitable for remote settings with poor infrastructure. The technically challenging, painful and risky diagnosis of meningitis and sleeping sickness through lumbar puncture is a good example. The gaps between field needs and available solutions are large, but, as we argue here, they can be effectively reduced by adopting a 'needs-based' approach to research and development and by making use of existing resources.

As with medicines for neglected diseases, the development of diagnostic tools for use in resource-poor settings is often thought to have little market incentive for private companies. Decision-making in the pharmaceutical and biomedical industries is increasingly driven by priority-setting based on expected market returns[5]. This priority-setting puts the needs of the company shareholders before those of the patient. The experience we document here shows how, by combining the specific needs identified by MSF in the field with existing scientific expertise, the development of appropriate diagnostic tools can be accelerated. By speeding up this process we can keep costs down, and thereby increase the likelihood that a test will be developed or marketed. Such opportunities should be attractive to both test providers and purchasers in the private and public sectors.

An example of such a needs-based product-development strategy is the development of a

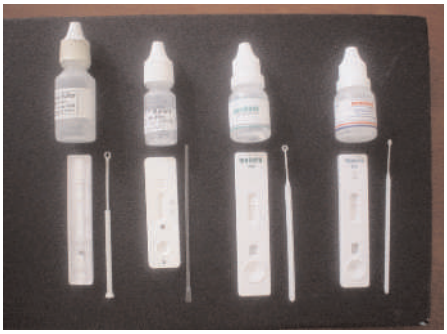
new rapid diagnostic test (RDT) for malaria that is now in the final stages of field evaluation. Currently, MSF performs more than 4 million malaria RDTs a year, mainly in Africa and Asia. Specific problems with existing tests were previously identified by MSF staff. For example, the current 'gold standard', smear microscopy, requires trained technicians and careful quality-control, which is not always possible in the field. Existing RDTs based on detecting the malaria parasite protein HRP2 in fingerprick blood were seen to be useful and cost-effective, but are limited because HRP2 proteins circulate for months in the blood after cure and therefore the test cannot distinguish between an old, resolved infection and a new one. Nor do they detect all strains of malaria.

In 2003, MSF decided to coordinate the development of an alternative test, by starting with a precise definition of what was needed in the field — what type of test, who would use it, and how the information obtained would be integrated into subsequent medical decisions. It is tempting to make the most elegant, informative and cutting-edge device. However, the design goal was a test most adapted to the setting in which it was to be used — mainly in malaria-endemic areas in Africa, where heat and humidity, ease of use and cost are important concerns. The needs in Asia are different: there is more than one endemic parasite species and different levels of infection and resistance in the populations that make additional information, such as the strain of parasite, desirable.

Everyone's happy

MSF brought together scientists, field doctors and manufacturers who applied their expertise to the development of an alternative test based on the detection of the malaria parasite enzyme pLDH in the blood. This test is more suited for diagnosing malaria in Africa than the HRP2 test because, among other things, pLDH levels drop rapidly with clearance of parasites, allowing clinicians to distinguish between patients who are still infected with malaria after treatment, and those in whom fever symptoms have another cause. The possibility of a pLDH test was identified by MSF from published papers on the characterization of a panel of pLDH monoclonal antibodies[6]. After several rounds of discussions to define the medical needs of field clinicians and the integration of the results into patient care, MSF contacted the US developer of the antibodies, Michael Makler of the company Flow Inc. in Portland, Oregon, to explore the possibility of using his reagents.

The initial feasibility of the project was tested by other leading scientists who gave advice and performed *in vitro* validation. The antibodies were then offered to three manufacturers who worked to optimize the test format for ease of use and performance, and developed three independent versions of the pLDH test. These were then evaluated in MSF field projects. Opening up the market to more than one company encouraged the manufacturers to pursue development of a quality product that is adapted to field conditions, while maintaining the price at an accessible level. The entire development process, from identification of diagnostic needs through to field evaluation, was completed in less than two years, at the relatively low cost of about €80,000 (US$100,000), most of which went into field trials and was provided by MSF. Development of a new test can typically cost many hundreds of thousands of dollars[7].



Malaria tests tailored for use in Africa.

This unusual development process has shown that products that are needed in the field, especially those for which there is not a 'traditional' or high-paying market, can still be developed in an efficient, commercially viable and mutually beneficial way. The development of this test differed from a typical diagnostic device in that low cost and field specifications were the main considerations from the outset, rather than market-driven (how much can we charge?) or technology-driven (what is the maximum information that we can deliver?) processes. The development team (MSF, Michael Makler, three different manufacturers, scientific and technical consultants, and field users) were guided at all times by these specifications. Thus, although all the players had their own motivations for participating, whether it was altruism, profit, need, curiosity or otherwise, all parties were working towards the same goal.

A successful model

The development of the malaria test built both on existing research (the use of pLDH as a marker for malaria infection) and existing technologies (immunochromatographic rapid tests). This created an efficient development model that we believe can be replicated elsewhere. In universities and industrial labs there are many −80 °C freezers or bottom drawers of filing cabinets containing antibodies, constructs or designs that have been shelved owing to lack of funding, interest or conflicting corporate or research priorities. MSF and others can act as partners in guiding the development of these 'leftover' products into appropriate tools.

But large doses of goodwill and unlimited access to freezers are not enough. In most cases, developing such tests requires cash and infrastructure, resources that are not always available. However, if the test is based on a solid assessment of the field needs and capabilities, it is more likely to be useful and the resources will be well spent. This happens when medical care drives the development of tests, rather than doctors being forced to adapt their medical care to the existing tools. The pLDH development model was a successful one, and it can and should be applied in other contexts.

MSF's experience during the development of this new malaria test shows how common interests can be fostered to bridge the gap between the needs of product developers and end users for the ultimate benefit of all involved. Given the long list of diseases with neglected diagnostics, there are many more opportunities to act and to make a difference. We appeal to scientists to respond to such opportunities by making existing reagents and ideas available for the development of diagnostic tests for these diseases. Such projects can make financial sense and have a huge impact on serious health issues, often without the enormous budgets of traditional development models.

We have described just one of many approaches needed to address the gaps in diagnostics; others include better use of existing reagents, training of local technicians in the field and a more creative and flexible approach to traditional product development. We recognize that there are other factors that limit the development of new tools. In many cases, intellectual-property restrictions pose a significant barrier. There are also important issues in ensuring the quality of the tests and in developing international standards for diagnostic tools. However, we have shown that alternative models that are realistic about the needs and limitations in the field, and that take account of the different motivations of the people involved, do work. By linking existing resources with user needs, we can encourage the development of crucial diagnostic tools, for the benefit of developers and patients alike. ■

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