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Keeping ahead of the resistance curve: product bundling to conserve artemisinin-based combination therapy



During recent years, malaria morbidity and mortality have substantially decreased.^{1,2} However, concurrently, resistance to artemisinin-based combination therapy and proliferation of substandard and counterfeit antimalarial drugs have continued to increase and subsequently threaten effective malaria control.²⁻⁴ Here we suggest that bundling of rapid diagnostic tests with artemisinin-based combination treatment could address these two closely related problems.

The global strategy to combat uncomplicated malaria relies on the widespread adoption of rapid diagnostic tests and the use of artemisinin-based combination treatment.^{2,3} Rapid diagnostic tests for malaria help with early and accurate diagnosis of infection (typically within 20 min) and are effective, with high sensitivity (80–95%) and specificity (85%) in malaria-endemic countries.^{2,5} The cost of a rapid diagnostic test ranges from US\$0.45 for a *Plasmodium falciparum* test to \$1.40 for an all-species test.⁴ Therefore, WHO guidelines recommend the use of these tests in these settings for the management of fever-like illness in children and adults.^{1,5}

Antimalarials have large (although not well quantified) selection pressures on malaria parasites, and evolving resistance to artemisinin has been reported in southeast Asia with growing concern that resistance might spread.³ Additionally, the common practice of presumptive use of artemisinin-based combination treatment to treat fevers in many clinical settings inevitably leads to overuse.^{2,6} With few alternative treatment options available, the conservation of this treatment is important and thus improved stewardship is key to slowing down resistance.^{1,2,5,6}

Bundling of medical products has been used successfully to improve health intervention delivery, as with the joint WHO-UNICEF policy statement on mass immunisation.⁷ The statement recommended the combination of vaccines, autodisposable syringes, and safety disposal boxes into one theoretical bundle for use in all mass-immunisation campaigns. A similar approach could conceivably be adapted for better antimalarial stewardship and include physical bundling of the two approaches for delivery to national control programmes.

The main aim of such a strategy would be to improve access to diagnostics and treatment while concurrently limiting excessive drug pressure in driving resistance through reductions in inappropriate prescription of artemisinin-based combination treatment. Bundled packages might also save costs for control programmes through fewer unnecessary prescriptions and more integrated diagnostic, treatment supply, and procurement chains. A bundling strategy would consist of three core elements: the alignment of financing mechanisms so that rapid diagnostic tests and artemisinin-based combination treatment can be funded and procured together; the epidemiological bundling based on local diagnostic and treatment needs; and the physical bundling of kits for delivery. This strategy might work well in public health care or pharmaceutical settings in which procurement and subsequent prescription of artemisinin-based combination treatment is subsidised or not directly linked to the income of the institution.

With wide variations in malaria endemicity, bundled packs would have to reflect the underlying epidemiology of target geographical areas. Ratios of rapid diagnostic tests to artemisinin-based combination treatment per pack would have to be adjusted to account for this as well as seasonal and treatment variations between paediatric and adult patient groups. In low transmission areas and seasons, several rapid diagnostic tests would be bundled per artemisinin-based combination treatment pack, and unused artemisinin-based combination components would be retained in storage until a positive rapid diagnostic test was obtained. In high transmission areas and seasons, fewer rapid diagnostic tests would need to be bundled per artemisinin-based combination treatment.

For rare or unexpected aberrations in local or national epidemiology (eg, an unusually long rainy season or an unexpected outbreak), a central repository of limited numbers of 1:1 ratio bundles could be stored for rapid deployment. In the private sector, the use of bundled products has already started to grow, with several bundled products and schemes now available.^{8,9} Concurrently, financing mechanisms, such as all-inclusive pricing for testing and appropriate treatment are also being explored and evaluated.¹⁰

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Panel: How bundling might work at a national level—supporting malaria control in Senegal

Senegal introduced rapid diagnostic tests for malaria in 2007 and testing rates rose rapidly from 4% to 86% by 2009. Concurrently, the prescription of artemisinin-based combination treatment fell throughout the period, from 73% of malaria-like febrile illness to 32%—approximating quite closely the number of confirmed malaria cases. As a result, about 500 000 unnecessary artemisinin-based combination treatment courses were avoided during the period.¹ These data suggest that for planning purposes at a national level, a 3:1 ratio of rapid diagnostic testing to artemisinin-based combination treatment would be an appropriate bundling strategy for Senegal.

Therefore, a standardised means of establishing the type and number of rapid diagnostic tests per treatment course of artemisinin-based combination treatment would need to be developed to support national malaria control programmes. The long product shelf-life of rapid diagnostic tests (18–24 months) means that worldwide mechanisms for supporting malaria control, such as Roll Back Malaria or the Global Fund, would be able to plan in advance how many bundles individual countries would require every year. This would support availability of an overall national supply that could be released periodically to account for local variations in incidence. The panel shows an example of how this might work in practice at a national level.

Illegal trade in counterfeit artemisinin-based combination treatment is a major problem in Asia and Africa, and the subset of counterfeits containing substandard antimalarial compounds might contribute to driving antimalarial resistance.¹¹ A cross-sectoral approach to illegal trade in counterfeit artemisinin-based combination treatment requires public, political, legal, and financial interventions, and the adoption of novel technological solutions.^{11,12}

Bundling could potentially contribute to combating counterfeit artemisinin-based combination treatment by adding extra layers of complexity and cost for counterfeiters (through the inclusion of a rapid diagnostic test in the pack). For example, the control line on the rapid diagnostic test strip would also have to be forged, hence when functional, could serve to reassure the patient and clinician that the bundled kit is genuine.

The next steps in exploring the feasibility of bundling rapid diagnostic tests with artemisinin-based combination treatment include broadening the

debate by engaging policy makers, industry, and other stakeholders, and then pilot use in the public health-care sector as is already being done in the private sector.⁹ These pilot studies would have to show improved uptake of rapid diagnostic tests and a reduction in inappropriate prescription of artemisinin-based combination treatment. Ultimately, if effective, sustainable economic models would need to be developed to increase equitable access. Therefore, improved stewardship through bundling of rapid diagnostic tests with artemisinin-based combination treatment could be one important development in improving global malaria control.

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We declare no competing interests.

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