February 2011 – SUPPORT Summary of a systematic review

What are the effects of using drugs packaged in unit doses to treat malaria?

Millions of people contract malaria each year. The WHO currently promotes artemisinin-based combination therapy (ACT) for treating uncomplicated malaria, but this may be more difficult for patients to adhere to correctly than other treatments.

Packaging a course of treatment in units of a single dose may be a more effective way of ensuring that patients take the correct dosage, and thus of increasing treatment success.

Key messages

- **The use of blister packs may improve adherence to treatment for malaria and may lead to slightly fewer treatment failures. No studies reported adverse events**
- **The use of sectioned polythene bags rather than bottled syrup may improve adherence to treatment in children under 5 years who have malaria. However, it is uncertain whether their use decreases treatment failures and whether it may lead to a higher number of minor adverse events**
- **The use of sectioned polythene bags rather than paper bags, probably improves adherence to treatment and may slightly decrease treatment failures in children over 7 years and adults with malaria. Their use may not lead to any difference in adverse events**
- **It is uncertain whether the use of sectioned polythene bags (compared with unsectioned bags) increase adherence or patient outcomes. No studies reported adverse events**

Who is this summary for?

Healthcare professionals and people making decisions concerning the implementation of unit-dose packaged for treating malaria.

! This summary includes:

- **Key findings** from research based on a systematic review
- **Considerations about the relevance of this research** for low- and middle-income countries

X Not included:

- Recommendations
- Additional evidence not included in the systematic review
- Detailed descriptions of interventions or their implementation

This summary is based on the following systematic review:

Orton LC, Barnish G. Unit-dose packaged drugs for treating malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD004614

What is a systematic review?

A summary of studies addressing a clearly formulated question that uses systematic and explicit methods to identify, select, and critically appraise the relevant research, and to collect and analyse data from the included studies.

SUPPORT – an international collaboration funded by the EU 6th Framework Programme to support the use of policy relevant reviews and trials to inform decisions about maternal and child health in low- and middle-income countries. www.support-collaboration.org

Glossary of terms used in this report: www.support-collaboration.org/summaries/explanations.htm

Background references on this topic: See back page.

Background

Millions of people contract malaria each year, mainly in areas such as sub-Saharan Africa, South-East Asia and South America.

The WHO currently promotes artemisinin-based combination therapy (ACT). Unless the drugs are coformulated, people are often required to follow a regimen that includes more than one antimalarial drug at a time. Such regimens may be more difficult to follow correctly than single therapies. If treatment responses relate to the dose and schedule of a therapy, non-adherence may reduce treatment benefits.

Packaging a course of treatment in units of a single dose may help to ensure better that the correct dosage is taken and thus to increase the success of treatment.

The packaging systems adopted by different countries and pharmaceutical companies vary widely. Some types of packaging, such as the the WHO-recommended blister packaging for artemisinin-based regimens, require certain levels and types of technology. Variations are also found in the products developed within this packaging type.

How this summary was prepared

After searching widely for systematic reviews that can help inform decisions about health systems, we have selected ones that provide information that is relevant to low- and middle-income countries. The methods used to assess the quality of the review and to make judgements about its relevance are described here: www.support-collaboration.org/summaries/methods.htm

Knowing what's not known is important

A good quality review might not find any studies from low- and middle-income countries or might not find any well-designed studies. Although that is disappointing, it is important to know what is not known as well as what is known.

About the systematic review underlying this summary

Review objective: To summarise the effects of unit-dose packaged treatment on treatment failure and treatment adherence in people with uncomplicated malaria

	What the review authors searched for	What the review authors found
Interventions	Randomised controlled trials (RCTs) and quasi-RCTs evaluating programmes that include unit-dose packaging of antimalarial drugs	1 RCT, 1 cluster RCT, and 3 quasi-RCTs evaluating labelled and boxed blister packs of chloroquine and primaquine tablets and capsules (2 studies) and simple, labelled and sectioned polythene bags of chloroquine tablets (3 studies)
Participants	People diagnosed with uncomplicated malaria infection	People with uncomplicated malaria confirmed clinically (2), microscopically (2), or using both methods (1)
Settings	Any setting	Outpatient health centres in China (2), Ghana (2) and Papua New Guinea (1)
Outcomes	Treatment failure, treatment adherence and adverse events	None of the trials reported on treatment failure but all reported on some of the following: parasitaemia, clinical symptoms, wellness of the child, cure according to medical notes and the perception of participants, and the recrudescence of infection. All 5 trials reported on treatment adherence. Adverse events were measured in 2 studies
Date of most recent search: February 2009		
Limitations: This is a good quality systematic review with only minor limitations		

Orton LC, Barnish G. Unit-dose packaged drugs for treating malaria. *Cochrane Database of Systematic Reviews* 2005, Issue 2. Art. No.: CD004614. http://dx.doi.org/10.1002/14651858.CD004614.pub2

Summary of findings

This review found five studies conducted in LMIC settings that evaluated and compared the use of labelled and boxed blister packs and simple, labelled and sectioned polythene bags, with the use of paper envelopes, bottled syrup or unsectioned bags. All studies measured adherence and some measure of treatment success (none measured treatment success as suggested by the WHO), but only two reported adverse events.

1) The use of blister-packed tablets and capsules compared with the provision of tablets and capsules in paper envelopes to improve adherence and patient outcomes in uncomplicated malaria

Two studies in adolescents and adults evaluated the use of boxed blister packs that had the drug name on the blister pack and inside the box. These packs were used for a 3-day course of the drug chloroquine and an 8-day course of primaquine, taken each day together from individual blister units.

➔ **The use of blister packs may improve adherence to treatment in malaria**

➔ **The use of blister packs may lead to slightly fewer treatment failures. No studies reported adverse events**

About the quality of evidence (GRADE)

⊕⊕⊕⊕
High: Further research is very unlikely to change our confidence in the estimate of effect.

⊕⊕⊕◯
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

⊕⊕◯◯
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

⊕◯◯◯
Very low: We are very uncertain about the estimate.

For more information, see last page

The use of blister packs compared with the use of paper envelopes

Patients or population: Uncomplicated malaria
Settings: Any setting
Intervention: Blister-packed tablets and capsules
Comparison: Tablets and capsules in paper envelopes

Outcomes	Comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Without blister-packs	**With blister-packs**			
Treatment failure	In one of the two studies, all participants (intervention and control) were aparasitaemic and asymptomatic at the end of the treatment period. In the other study, one of the 57 participants in the comparison group had recrudesced at day 88 (there were no such occurrences in the intervention group)		Not estimable	596 (2 studies)	⊕⊕◯◯ Low
Treatment non-adherence	**18 per 100**	**3 per 100** (1 to 12)	RR **0.14** (0.07 to 0.30)	596 (2 studies)	⊕⊕◯◯ Low
Adverse events	None of the studies measured adverse events		Not estimable	596 (2 studies)	⊕◯◯◯ Very low

CI: Confidence interval RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)
*Illustrative comparative risks. The assumed risk WITHOUT the intervention is based on non adherence rates in the 2 studies summarised in this table. The corresponding risk WITH the intervention (and it's 95% confidence interval) are based on the overall relative effect (and its 95% confidence interval).

2) The provision of tablets in sectioned polythene bags compared with the provision of drugs in bottled syrup form to improve adherence and patient outcomes in uncomplicated malaria

One study in children aged 0 to 5 years, evaluated the use of hermetically sealed, sectioned polythene bags containing daily doses of chloroquine tablets (labelled '1', '2', or '3' to indicate the day of dosage) and compared this with the provision of the same drug in bottled syrup form.

➔ **The use of sectioned polythene bags may improve adherence to treatment in malaria**

➔ **It is uncertain whether the use of sectioned polythene bags decreases treatment failures. It is also uncertain whether their use may lead to an increase in the number of minor adverse events in malaria treatment**

The use of sectioned polythene bags compared with bottled syrup

Patients or population: Children with uncomplicated malaria
Settings: Any setting
Intervention: Tablets in sectioned polythene bags
Comparison: Bottled syrup

Outcomes	Comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Without polythene bags	**With polythene bags**			
Treatment failure	Most participants in both the groups were considered by their caregivers to have fully recovered by the end of the treatment period		Not estimable	299 (1 study)	⊕◯◯◯ Very low
Treatment non-adherence	**58 per 100**	**10 per 100** (6 to 13)	RR **0.16** (0.09 to 0.26)	299 (1 study)	⊕⊕◯◯ Low
Adverse events	Of the 155 participants receiving tablets, 28 vomited some of the medication and six vomited all the tablets		Not estimable	299 (1 study)	⊕⊕◯◯ Low

CI: Confidence interval RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)
*Illustrative comparative risks. The assumed risk WITHOUT the intervention is based on the study summarised in this table. The corresponding risk WITH the intervention (and it's 95% confidence interval) are based on the overall relative effect (and its 95% confidence interval).

3) The provision of tablets in sectioned polythene bags compared with the provision of the tablets in paper envelopes to improve adherence and patient outcomes in uncomplicated malaria

One study of adults and children (7+ years) compared the use of hermetically sealed, sectioned polythene bags containing daily doses of chloroquine tablets (labelled '1', '2' or '3' to indicate the day of dosage), with the same dosage provided in paper envelopes.

➔ **The use of sectioned polythene bags probably improves adherence to treatment in malaria**

➔ **The use of sectioned polythene bags may decrease slightly treatment failure and may not lead to any difference in adverse events**

The use of sectioned polythene bags compared with the use of paper envelopes

Patients or population: Uncomplicated malaria
Settings: Any setting
Intervention: Tablets in sectioned polythene bags
Comparison: Tablets and capsules in paper envelopes

Outcomes	Comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Without polythene bags	**With polythene bags**			
Treatment failure	The wellness of most participants improved at the end of treatment (intervention: 152 improved, 13 unchanged, 2 worsened; control: 143 improved, 4 unchanged, 5 worsened)		Not estimable	319 (1 study)	⊕⊕◯◯ Low
Treatment non-adherence	**40 per 100**	**19 per 100** (13 to 27)	RR **0.46** (0.31 to 0.66)	319 (1 study)	⊕⊕⊕◯ Moderate
Adverse events	Similar incidence of itching, dizziness and other adverse events		Not estimable	319 (1 study)	⊕⊕◯◯ Low

CI: Confidence interval RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)
*Illustrative comparative risks. The assumed risk WITHOUT the intervention is based on the study summarised in this table. The corresponding risk WITH the intervention (and it's 95% confidence interval) are based on the overall relative effect (and its 95% confidence interval).

4) The provision of tablets in sectioned polythene bags compared with the use of polythene bags (unsectioned) to improve adherence and patient outcomes in uncomplicated malaria

One study in adults evaluated a 3-day regimen of drugs were administered in sealed, clear and sectioned polythene bags stapled to a card base with the daily dosage of tablets in each colour-coded section, and the name of the drugs and instructions written below each section.

➔ **It is uncertain whether the use of sectioned polythene bags (compared with the use of unsectioned bags) increases adherence or patient outcomes. No studies reported adverse events**

The use of sectioned polythene bags compared with polythene bags (unsectioned)

Patients or population: Uncomplicated malaria
Settings: Any setting
Intervention: Tablets in sectioned polythene bags
Comparison: Polythene bags (unsectioned)

Outcomes	Comparative risks*		Relative effect (95% CI)	Number of participants (studies)	Quality of the evidence (GRADE)
	Without sectioned bags	**With sectioned bags**			
Treatment failure	No significant difference in the cure rate at day four (intervention 77/91 compared with control 96/112)		Not estimable		⊕◯◯◯ Very low
Treatment non-adherence	**5 per 100**	**2 fewer per 100 (from 5 fewer to 9 more)**	RR **0.77** (0.26 to 2.27)		⊕◯◯◯ Very low
Adverse events	The study did not measure adverse events		Not estimable		⊕◯◯◯ Very low

CI: Confidence interval RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)
*Illustrative comparative risks. The assumed risk WITHOUT the intervention is based on the study summarised in this table. The corresponding risk WITH the intervention (and it's 95% confidence interval) are based on the overall relative effect (and its 95% confidence interval).

Relevance of the review for low- and middle-income countries

➔ Findings	▷ Interpretation*
APPLICABILITY	
➔ The review identified five studies, all in LMIC settings, that evaluated the use of unit-dose packaging to improve adherence in children and adults with uncomplicated malaria ➔ The use of unit-dose packaged treatments probably improves adherence. However, it is very uncertain whether there are any beneficial effects in patient outcomes or adverse events	▷ *These findings related to the implementation of interventions to improve medication adherence in uncomplicated malaria, suggest that such interventions should be viewed with caution by those reponsible for decision making. This is because there is a high degree of uncertainty about their effects on patient outcomes, adverse events and costs*
EQUITY	
➔ The studies did not directly address the issue of equity	▷ *The causes of poor adherence (including. poor memory, illiteracy, and an inability to pay for treatment) often impact disadvantaged populations more. Interventions to increase adherence might therefore aim to help these populations selectively to achieve the theoretical benefits of effective medication* ▷ *Unfortunately, these theoretical effects remain unproven*
ECONOMIC CONSIDERATIONS	
➔ The included studies provided no data about the costs of the interventions	▷ *Some types of packaging, such as the blister packaging recommended by the WHO for artemisinin-based regimens, require certain levels of technology,* ▷ *The cost-benefit effects of these interventions is difficult to anticipate based on the information available*
MONITORING & EVALUATION	
➔ Self-reporting was used to measure adherence in the majority of studies, or other methods were used that were also not sensitive ➔ This review found evidence that some interventions may lead to better adherence, but they did not measure patient outcomes adequately ➔There is ittle information about adverse events or costs in the existing studies ➔None of the studies addressed parasite drug resistance	▷ *Measuring adherence is a complex task and the methods used frequently to do this (such as self-reporting) are not sensitive. Objective measures provide a more accurate measure of true adherence but they are more expensive* ▷ *Future research should focus on the most promising interventions* ▷ *It simply cannot be assumed that measures to increase adherence do more good than harm even if they increase adherence* ▷ *Ensuring optimal treatment adherence may also help to slow the development of parasite drug resistance by ensuring that patients have the correct drug concentrations in their blood and are cured quickly*

*Judgements made by the authors of this summary, not necessarily those of the review authors, based on the findings of the review and consultation with researchers and policymakers in low- and middle-income countries. For additional details about how these judgements were made see: http://www.support-collaboration.org/summaries/methods.htm

Additional information

Related literature

Haynes RB, Ackloo E, Sahota N, McDonald HP, Yao X. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews 2008, Issue 2. Art. No.: CD000011

Horne R, Weinman J, Barber N, Elliot R, Morgan M. Concordance, adherence and compliance in medicine taking: a scoping exercise. London: NCCSDO; 2005.

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Conflict of interest

None declared. For details, see: www.support-collaboration.org/summaries/coi.htm

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Keywords

All Summaries: evidence-informed health policy, evidence-based, systematic review, health systems research, health care, low- and middle-income countries, developing countries, primary health care, malaria, unit-dose packaging, medication adherence, medication compliance, medication non-compliance, medication non-adherence, patient compliance, treatment refusal.

About quality of evidence (GRADE)

The quality of the evidence is a judgement about the extent to which we can be confident that the estimates of effect are correct. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the type of study design (randomised trials versus observational studies), the risk of bias, the consistency of the results across studies, and the precision of the overall estimate across studies. For each outcome, the quality of the evidence is rated as high, moderate, low or very low using the definitions on page 3.

For more information about GRADE:
www.support-collaboration.org/summaries/grade.htm

SUPPORT collaborators:

The Alliance for Health Policy and Systems Research (HPSR) is an international collaboration aiming to promote the generation and use of health policy and systems research as a means to improve the health systems of developing countries. www.who.int/alliance-hpsr

The Cochrane Effective Practice and Organisation of Care Group (EPOC) is a Collaborative Review Group of the Cochrane Collaboration: an international organisation that aims to help people make well informed decisions about health care by preparing, maintaining and ensuring the accessibility of systematic reviews of the effects of health care interventions.
www.epocoslo.cochrane.org

The Evidence-Informed Policy Network (EVIPNet) is an initiative to promote the use of health research in policymaking. Focusing on low- and middle-income countries, EVIP-Net promotes partnerships at the country level between policy-makers, researchers and civil society in order to facilitate both policy development and policy implementation through the use of the best scientific evidence available. www.evipnet.org

For more information:
www.support-collaboration.org

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