March 2017 – 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 for treating uncomplicated malaria, but this may be more difficult for patients to correctly adhere to 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. In this approach, drugs to be taken together are packaged adjacent to each other, sometimes with colours or other markers to show that the drugs should be taken together.

Key messages

➔ **No studies measured treatment failure on or by day 28 after initiation of treatment, which was the primary outcome in this review.**

➔ **The use of blister packs compared to paper envelopes for antimalarial drugs may improve adherence to treatment and may slightly improve clinical outcomes. No studies reported adverse events.**

➔ **The use of sectioned polythene bags compared with bottled syrup may improve adherence to treatment in children under 5 years who have malaria, but may increase vomiting. It is uncertain whether there is a difference in clinical outcomes.**

➔ **The use of sectioned polythene bags compared to paper envelopes for antimalarial drugs probably improves adherence to treatment and may slightly improve clinical outcomes in children over 7 years and adults with malaria. Their use may lead to little if any difference in adverse events.**

➔ **It is uncertain whether the use of sectioned compared to unsectioned polythene bags leads to a difference in adherence, clinical outcomes, or adverse events.**

Who is this summary for?

People making decisions concerning the implementation of unit-dose packaged drugs for treating malaria

! This summary includes:

- **Key findings** from research based on a systematic review
- **Considerations about the relevance of this research** for low-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 Syst Rev 2005; (2):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 was an international project to support the use of policy relevant reviews and trials to inform decisions about maternal and child health in low- and middle-income countries, funded by the European Commission (FP6) and the Canadian Institutes of Health Research.

Glossary of terms used in this report: www.supportsummaries.org/glossary-of-terms

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. 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 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-income countries. The methods used to assess the reliability of the review and to make judgements about its relevance are described here: www.supportsummaries.org/how-support-summaries-are-prepared/

Knowing what's not known is important

A reliable review might not find any studies from low-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.

A lack of evidence does not mean a lack of effects. It means the effects are uncertain. When there is a lack of evidence, consideration should be given to monitoring and evaluating the effects of the intervention, if it is used.

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

Types of	What the review authors searched for	What the review authors found
Study designs & Interventions	Randomised trials and quasi-randomised trials evaluating programmes that include unit-dose packaging of antimalarial drugs	1 randomised trial, 1 cluster-randomised trial, and 3 quasi-randomised trials 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 on or by day 28 after initiation of treatment (primary outcome), other clinical measures, 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 well-conducted systematic review with only minor limitations		

Orton LC, Barnish G. Unit-dose packaged drugs for treating malaria. Cochrane Database Syst Rev 2005; (2):CD004614

Summary of findings

This review found five studies conducted in low- and middle-income countries 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 the impacts of treatment. No studies measured treatment failure as defined in the review. Only two studies 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 compared to paper envelopes for antimalarial drugs may improve adherence to treatment and may slightly improve clinical outcomes. The certainty of this evidence is low.**

➔ **No studies measured treatment failure or reported adverse events.**

About the certainty of the evidence (GRADE) *

⊕⊕⊕⊕
High: This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⊕⊕⊕◯
Moderate: This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⊕⊕◯◯
Low: This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⊕◯◯◯
Very low: This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

* This is sometimes referred to as 'quality of evidence' or 'confidence in the estimate'.

† Substantially different = a large enough difference that it might affect a decision

See last page for more information.

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

People Uncomplicated malaria
Settings Any setting
Intervention Blister-packed tablets and capsules
Comparison Tablets and capsules in paper envelopes

Outcomes	Absolute effect* Without blister-packs	Absolute effect* With blister-packs	Relative effect (95% CI)	Certainty of the evidence (GRADE)
Treatment failure on or by day 28	None of the studies measured treatment failure.		-	-
Other clinical outcomes	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	⊕⊕◯◯ Low
Treatment non-adherence	18 per 100	3 per 100	RR 0.14 (0.07 to 0.30)	⊕⊕◯◯ Low
	Difference: 15 fewer patients per 100 failed to adhere to treatment (Margin of error: 6 to 17 fewer per 100)			
Adverse events	None of the studies measured adverse events		-	-

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The 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 the 95% confidence interval for the difference) is 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 compared to bottled syrup may improve adherence to treatment in malaria, but may increase vomiting. The certainty of this evidence is low.**

➔ **Treatment failure was not measured and it is uncertain whether there is a difference in clinical outcomes. The certainty of this evidence is very low.**

The use of sectioned polythene bags compared with bottled syrup

People Children with uncomplicated malaria
Settings Any setting
Intervention Tablets in sectioned polythene bags
Comparison Bottled syrup

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Without polythene bags	**With polythene bags**		
Treatment failure on or by day 28	The study did not measure treatment failure		-	-
Other clinical outcomes	Most participants in both the groups were considered by their caregivers to have fully recovered by the end of the treatment period		Not estimable	⨁◯◯◯ Very low
Treatment non-adherence	58 per 100	10 per 100	RR 0.16 (0.09 to 0.26)	⨁⨁◯◯ Low
	Difference: 48 fewer patients per 100 failed to adhere to treatment (Margin of error: 45 to 52 fewer per 100)			
Adverse events	Of the 155 participants receiving tablets, 28 vomited some of the medication and six vomited all the tablets		Not estimable	⨁⨁◯◯ Low

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The risk WITHOUT the intervention is based on the study summarised in this table. The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is 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 compared to paper envelopes for antimalarial drugs probably improves adherence to treatment. The certainty of this evidence is moderate.**

➔ **The use of sectioned polythene bags may slightly improve clinical outcomes and may lead to little if any difference in adverse events. The certainty of this evidence is low.**

➔ **Treatment failure was not measured.**

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

People Uncomplicated malaria
Settings Any setting
Intervention Tablets in sectioned polythene bags
Comparison Tablets and capsules in paper envelopes

Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	Without polythene bags	**With polythene bags**		
Treatment failure on or by day 28	The study did not measure treatment failure		-	-
Other clinical outcomes	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	⨁⨁◯◯ Low
Treatment non-adherence	40 per 100	19 per 100	RR 0.46 (0.31 to 0.66)	⨁⨁⨁◯ Moderate
	Difference: 21 fewer patients per 100 failed to adhere to treatment (Margin of error: 13 to 27 fewer per 100)			
Adverse events	Similar incidence of itching, dizziness and other adverse events		Not estimable	⨁⨁◯◯ Low

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The risk WITHOUT the intervention is based on the study summarised in this table. The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is 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 unsectioned polythene bags to improve adherence and patient outcomes in uncomplicated malaria

One study in adults evaluated a 3-day regimen of drugs 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 improves clinical outcomes. The certainty of this evidence is very low.**

➔ **No studies reported treatment failure or adverse events.**

The use of sectioned polythene bags compared with unsectioned polythene bags

People Uncomplicated malaria chloroquine tablets, that included sulphadoxine-pyrimethamine
Settings Any setting
Intervention Tablets in sectioned polythene bags
Comparison Polythene bags (unsectioned)

Outcomes	Absolute effect* Without sectioned bags	Absolute effect* With sectioned bags	Relative effect (95% CI)	Certainty of the evidence (GRADE)
Treatment failure on or by day 28	The study did not measure treatment failure		-	-
Other clinical outcomes	It is uncertain whether the intervention improves cure rates at day four (intervention 77/91 compared with control 96/112) because the certainty of the evidence is very low		Not estimable	⨁◯◯◯ Very low
Treatment non-adherence	5 per 100	3 per 100	RR 0.77 (0.26 to 2.27)	⨁◯◯◯ Very low
	Difference: 2 fewer patients per 100 failed to adhere to treatement (Margin of error: 5 fewer to 9 more per 100)			
Adverse events	The study did not measure adverse events		-	-

Margin of error = Confidence interval (95% CI) RR: Risk ratio GRADE: GRADE Working Group grades of evidence (see above and last page)

* The risk WITHOUT the intervention is based on the study summarised in this table. The corresponding risk WITH the intervention (and the 95% confidence interval for the difference) is based on the overall relative effect (and its 95% confidence interval).

Relevance of the review for low-income countries

➔ Findings	▷ Interpretation*
APPLICABILITY	
➔ **The review identified five studies, all in low- and middle-income country 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 uncertain whether there are any beneficial effects on patient outcomes or adverse events**.	▷ *These findings may be applicable in other low-income country settings, but it is not clear which types of unit-dose packaging might be best in different settings, such as rural areas, or for different population groups.* ▷ *It is not clear whether these impacts would be replicated when implementing unit-dose packaging in routine health services (rather than in the context of a trial).*
EQUITY	
➔ **The studies did not directly address impacts on equity.**	▷ *Factors affecting adherence (such as low levels of literacy, inadequate treatment information and an inability to pay for ongoing treatment) may impact more on disadvantaged populations. Interventions to increase adherence might therefore benefit these populations, particularly if these interventions address important barriers to adherence for these groups.*
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 equipment that may be expensive to purchase.* ▷ *The benefits of these interventions in relation to their costs are difficult to assess from the information available.*
MONITORING & EVALUATION	
➔ **Self-reporting or similar approaches were used to measure adherence in the majority of studies** ➔ **This review found evidence that some interventions may lead to better adherence, but the studies did not measure patient outcomes adequately.** ➔ **Little information on adverse events or costs is available from existing studies.** ➔ **None of the studies addressed parasite drug resistance.**	▷ *Measuring adherence is a complex task and the methods frequently used to do this (such as self-reporting) may not always be reliable. Studies need to consider how best to assess adherence for particular groups of people.* ▷ *Future research should focus on the most promising interventions and should assess patient outcomes as well as treatment adherence.* ▷ *Adverse events and costs should be assessed in future studies and where these interventions are implemented at scale.* ▷ *Ensuring optimal treatment adherence may also help to slow the development of parasite drug resistance. Studies should consider whether it would be useful to measure parasite drug resistance.*

*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-income countries. For additional details about how these judgements were made see: www.supportsummaries.org/methods

Additional information

Related literature

Haynes RB, Ackloo E, Sahota N, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev 2008 (2): CD000011

Horne R, Weinman J, Barber N, et al. 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.supportsummaries.org/coi

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About certainty of the evidence (GRADE)

The "certainty of the evidence" is an assessment of how good an indication the research provides of the likely effect; i.e. the likelihood that the effect will be substantially different from what the research found. By "substantially different" we mean a large enough difference that it might affect a decision. These judgements are made using the GRADE system, and are provided for each outcome. The judgements are based on the study design (randomised trials versus observational studies), factors that reduce the certainty (risk of bias, inconsistency, indirectness, imprecision, and publication bias) and factors that increase the certainty (a large effect, a dose response relationship, and plausible confounding). For each outcome, the certainty of the evidence is rated as high, moderate, low or very low using the definitions on page 3.

For more information about GRADE: www.supportsummaries.org/grade

SUPPORT collaborators:

The Cochrane Effective Practice and Organisation of Care Group (EPOC) is part of the Cochrane Collaboration. The Norwegian EPOC satellite supports the production of Cochrane reviews relevant to health systems in low- and middle-income countries . www.epocoslo.cochrane.org

The Evidence-Informed Policy Network (EVIPNet) is an initiative to promote the use of health research in policymaking in low- and middle-income countries. www.evipnet.org

The Alliance for Health Policy and Systems Research (HPSR) is an international collaboration that promotes the generation and use of health policy and systems research in low- and middle-income countries. www.who.int/alliance-hpsr

Norad, the Norwegian Agency for Development Cooperation, supports the Norwegian EPOC satellite and the production of SUPPORT Summaries. www.norad.no

The Effective Health Care Research Consortium is an international partnership that prepares Cochrane reviews relevant to low-income countries. www.evidence4health.org

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