Guideline for malaria prevention through vector control

Malaria Policy Advisory Committee Meeting

Geneva, Switzerland

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Global **Malaria** Programme

World Health Organization

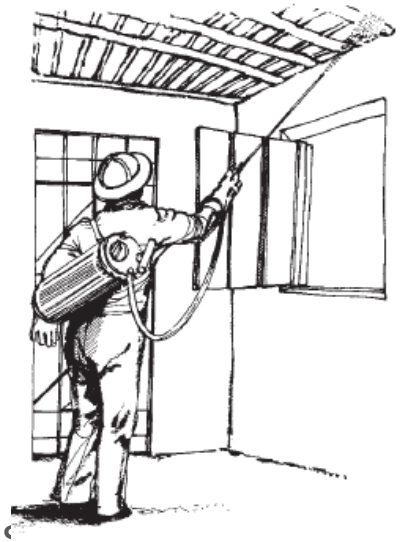
Objectives of the Guidelines

- To provide evidence-based recommendations for the effective implementation of each of the vector control options currently available for malaria prevention and control;
- To inform and guide technical decisions on the appropriate choice(s) of vector control options for malaria prevention and control in endemic countries;
- To support the development of evidence-based national malaria vector control policies and strategies by WHO Member States.

Implicit objectives of the Guidelines

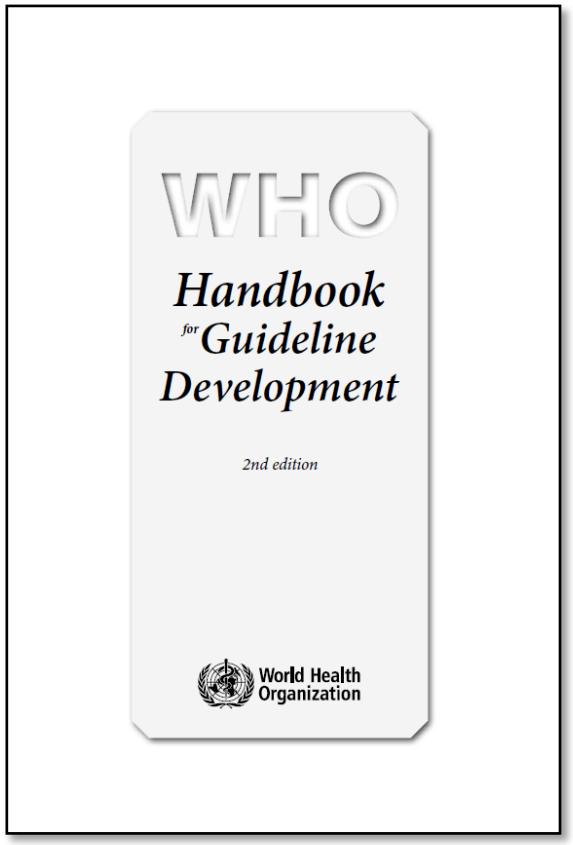
- To facilitate the use of WHO guidance by bringing together a large number of existing guidance documents on malaria vector control into one document;
- To inform a research agenda/workplan in support of the 2nd edition of the guidelines by:
  - identify gaps in evidence that prevent development of guidance or weaken current recommendations
  - identifying actions required to strengthen the evidence-base that supports WHO guidance

Scope



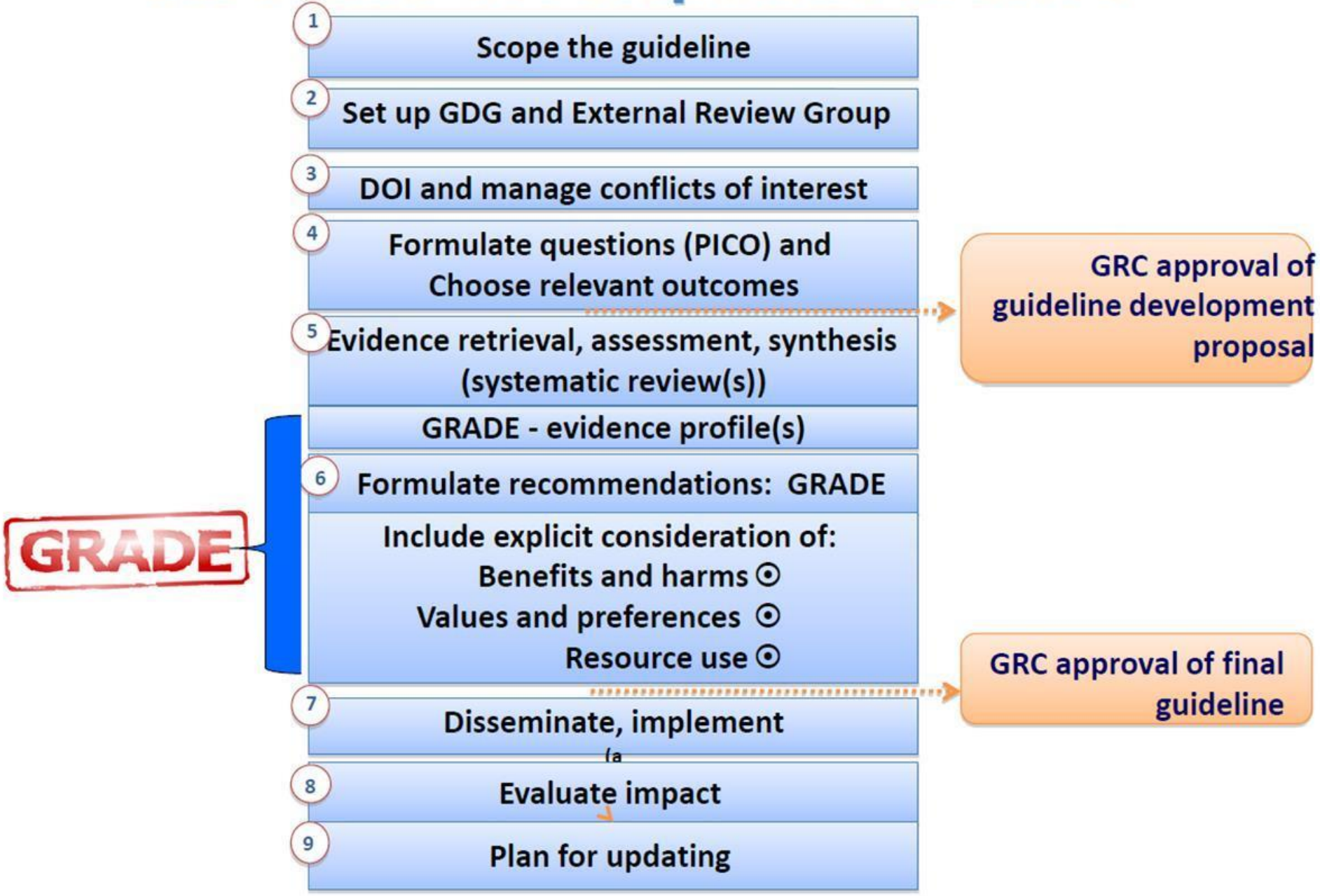
- Core Interventions
  - Indoor residual spraying (IRS)
  - Insecticide treated nets (ITNs, LLINs)
- Supplementary Interventions
  - Larval source management (LSM)
  - Space spraying
  - Topical repellents, treated clothing & spatial repellents
  - Housing improvements
- Settings and programmatic factors affecting selection and deployment of vector control interventions
  - Residual transmission
  - Epidemics & humanitarian emergencies
  - Migrant populations & populations engaged in high-risk activities
- Implementation challenges

Process

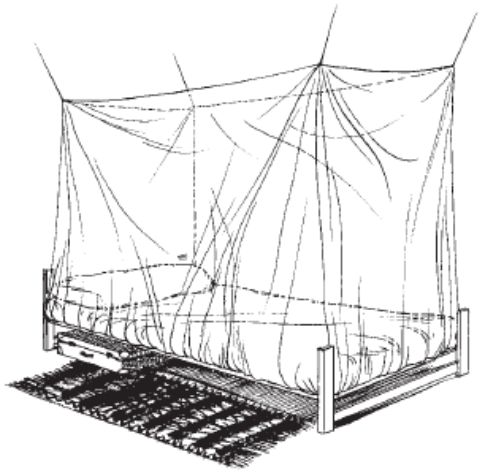


Available at: http://www.who.int/publications/guidelines/handbook_2nd_ed.pdf

Guideline development at WHO



PICO* question; ITN example



Question: Are ITNs effective in reducing transmission compared with no ITNs, or untreated nets?

Studies included: Individual randomized controlled trials (RCTs) and cluster RCTs (cRCT).

Population: Children and adults living in malaria transmission settings.

Intervention: Bed nets or curtains treated with a synthetic pyrethroid insecticide at a minimum target impregnation dose recommended by the WHO. No distinction was made between insecticide-treated bed nets and door/window/eave/wall curtains.

Comparator: Populations provided with either no net or with an untreated net.

Primary outcome: Child mortality from all causes.

Secondary outcomes: Parasite prevalence, uncomplicated clinical episodes, severe disease

* PICO: Population, Intervention (or Exposure), Comparator, Outcome; four elements to consider in any question governing a systematic search of the evidence

** Note: Systematic review of exp. hut data comparing mortality and blood-feeding outcomes for pyrethroid-only with PBO nets is ongoing. Potential to include results in 1st edition.

Timeline

September 2016	Concept presented to MPAC & endorsed
October 2016	Proposal submitted to WHO Guidelines Review Committee (GCR). Document was reviewed, responses sent back to GRC, and proposal was approved
March 2017	Guideline Developing Group (VCTEG) was convened to reach consensus on the PICO questions and Outcomes
	Cochrane Infectious Diseases Group commissioned to undertake systematic reviews and develop summary of findings tables
	MPAC updated on progress
July 2017	Lead writer contracted. Development of document structure started, based on structure of malaria case management guidelines
October 2017	Evidence summaries received from Cochrane Group
November 2017	VCTEG reviewed evidence summaries and developed GRADE tables using GRADE Pro (https://gradepro.org/)
Dec 2017 to now	Guidelines written, disseminated for initial reviews, updated and edited
April 2018	MPAC review
May 2018	GRC submission
Q3 2018	Guideline Publication

Research agenda / workplan for 2nd edition

- Systematic review of data on the impact of IRS interventions from lower quality (non-RCT) studies. Conduct similar work in the area of LSM.
- To develop a chapter to guide the collection of cost data alongside research studies for inclusion in the trial design manual recently issued by WHO on behalf of VCAG (Work ongoing)
- Update systematic review of costs and cost-effectiveness data (i.e. White et al. 2011) of all vector control interventions to complement the evidence base upon which recommendations are developed and identify knowledge gaps in these areas
- Potentially supplemented the review on cost-effectiveness through generation of additional evidence / conducting further analysis
- To review current evidence on resource use and draft expanded GRADE tables that include this information as an initial step to enhance guidance on prioritization of interventions
- To identify guidance needs, as well as capacity and resource requirements, associated with country-level prioritization with a view of supporting countries develop their own resource need and budget impact assessments.
- To develop further guidance on the use of interventions and new tools in special situations

Cost-effectiveness example

4.3 Cost-effectiveness

The EG assessed the results of a cost-effectiveness analysis (CEA) conducted to model the incremental cost-effectiveness of adding delamanid to existing WHO-recommended MDR-TB regimens. This CEA was undertaken for different settings to allow for variation among countries across income level, the model of care used for MDR-TB treatment, and background patterns of drug resistance. It focused on the direct benefits to patients, but did not attempt to assess the indirect (and acquired) transmission benefits, nor did it assess the broader economic benefits to patients or society.

Since several analyses were conducted by the manufacturer to assess efficacy (see above), a sensitivity analysis was performed on the cost-effectiveness of delamanid when different trial data and assumptions about the translation of trial results to current practice were applied. Results showed that delamanid would be cost-effective in most environments studied. However, this interpretation needs to take into account the quality of clinical evidence as assessed by the EG (i.e. if the quality of clinical evidence is viewed as low, then likewise the evidence supporting cost-effectiveness should be regarded as low), as well as all limitations related to the assumptions made above. Of note, in settings where cure/treatment success rate is currently high, delamanid may not be cost-effective, as it may result in limited additional benefit. However, the incremental cost of delamanid introduction will not only depend on price, but also on the cost savings for retreatment as a result of an expected reduction in treatment failures. Using a conservative approach, delamanid was thus found to be cost-effective in most settings, but the quality of this evidence was considered very low, and further work would be needed to evaluate cost-effectiveness and to test the robustness of the assumptions in various settings.

From: Section 4, Evidence base for policy formulation. In: The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. WHO, 2014.

Resource use example

	Criteria	Judgments	Research evidence	Additional considerations
Resource use	**Are the resources required small?**	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ● Varies	Using a conservative approach, and based on limited evidence (and therefore likely to be uncertain), delamanid is found to be cost-effective in most settings. The two main exceptions are in settings with a very high current cure/treatment success rate, where defaults rates are high; and low income settings, where uncertainty about outcomes impacts cost-effectiveness. In these settings further work needs to be done to evaluate cost-effectiveness, in particular examining any impact on transmission, and improving the assessment of uncertainty. Of note, the application of different trial results impacts cost-effectiveness, and may in some cases double the incremental cost-effectiveness ratio. In all cases, further country based work, placing delamanid in a broader framework of investment prioritisation including considerations on equity and budget impact would be recommended from an economic perspective before country adoption.	The expert panel took the perspective of a TB programme (costs) and focused on direct benefits to patients . Indirect transmission benefits were NOT considered. The analysis excludes any broader economic benefits (productivity) to patients and society beyond health benefits. One of the key considerations is that defaulters are accounted for and there is an assumption that 80% die when defaulted. The analysis is based on drug cost parameters provided by the manufacturer for the cost effectiveness analysis.
	Is the incremental cost small relative to the net benefits?	○ No ○ Probably no ○ Uncertain ○ Probably yes ○ Yes ● Varies	Using a simple model, conservative approach, based on limited evidence (and therefore likely to be uncertain), delamanid in addition to the WHO recommended baseline regimen is found to be cost-effective in most settings. The two main exceptions are in settings with a very high current cure/treatment success rate, where defaults rates are high; and low income settings, where uncertainty about outcomes impacts cost-effectiveness. Results of modelling in various country settings show that the application of different trial results do not move the ICER above the willingness to pay thresholds in any of these but one (Nepal). However they do make a 2-3 fold difference in the ICER. Of note, the application of different trial results impacts cost-effectiveness, and may in some cases double the incremental cost-effectiveness ratio. In all cases, further country based work, placing delamanid in a broader framework of investment prioritization including considerations on equity and budget impact would be recommended from an economic perspective before country adoption. Further work is also required to fully take into account transmission and patient cost consequences and to understand the efficacy of delamanid in settings where the OBR already achieves high cure/treatment success rates. Further work is required also in low income settings to fully take into account transmission and patient cost consequences.	Willingness to pay (WTP) thresholds (one GNI per capita) and DALYs were used. There are many sources of uncertainty: parameters (costs, prices, efficacy, long term outcomes) Mortality differences are based on assumptions in the original trial (204) and this is the key driving factor for cost-effectiveness - based on assumptions including that it is based on the modified Intention to treat analysis. There is likely imprecision in the cost effectiveness estimates because of the imprecision of the mortality estimates. It is also based on the assumption that 80% of defaulters are dying. ICER increased up to threefold in sensitivity analyses but cost effectiveness is maintained based on WTP thresholds.

From: Table 5, The GRADE evidence to recommendation, p. 42. In: The use of delamanid in the treatment of multidrug-resistant tuberculosis. Interim policy guidance. WHO, 2014.

Resource requirements example

Table 3.7 Main resource requirements for adopting new definitions of the latent and active phases of the first stage of labour

Resource	Description
Training	▪ Practice-based training for health care providers to increase knowledge on in-hospital and outpatient supportive care for the latent phase of the first stage of labour
Supplies	▪ Revised training manuals and clinical protocols for health care providers and those in pre-service training ▪ Educational materials for women on what comprises onset of the latent and active phases, and when to go to a facility for assessment ▪ Revised paper partograph indicating the starting point of the active phase
Infrastructure	▪ Where all women are directly admitted to the hospital regardless of the phase of labour, sufficient beds should be provided in the maternity/antenatal ward where necessary supportive care (e.g. pain relief) can be provided to women prior to reaching cervical dilatation of 5 cm
Supervision and monitoring	▪ Ongoing supervision and monitoring with regular auditing and review of outcomes related to application of the new definition of the active phase

From: Intrapartum care for a postive childbirth experience. WHO Recommendations. WHO, 2014.

Acknowledgements

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Questions to MPAC

- Do the draft guidelines meet their objectives?
- Does the research / workplan agenda capture the key elements required to develop an updated / improved 2nd versions?
- To what extent should existing GMP recommendations be updated before publication of the 1st edition of the guidelines?