



health

Department:
Health
REPUBLIC OF SOUTH AFRICA



**South African National Essential Medicine List
Primary Health Care Medication Review Process
Component: Gastrointestinal conditions**

MEDICINE MOTIVATION:

1. Executive Summary

<p>Date: 31 January 2017 Medicine (INN): Benzimidazoles Medicine (ATC): P02CA Indication (ICD10 code): Patient population: Children \geq 1 year of age and adults Prevalence of condition: Level of Care: Primary Health Care Prescriber Level: Nurse prescribers Current standard of Care: Mebendazole Efficacy estimates: (preferably NNT) Motivator/reviewer name(s): Primary Health Care Committee (motivator); Ms TD Leong (reviewer) PTC affiliation: n/a</p>
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2. Name of author(s)/motivator(s):

Author: Ms TD Leong*
Motivator(s): Primary Health Care Committee (2016)

3. Author affiliation and conflict of interest details:

*National Department of Health, Secretariat for the Primary Health Care Technical Sub-Committee of NEMLC, 2016.
Conflicts of interest: None

4. Introduction/ Background

Soil-transmitted helminth infestation is common throughout South Africa, particularly in low-altitude, coastal areas, where *Ascaris lumbricoides* (roundworm) and *Trichuris trichiura* (whipworm) infestations are more prevalent.^{i ii iii iv} *Necator americanus* (hookworm) is less common and mostly confined to the sandy coastal plain of KwaZulu-Natal, some sandy areas further inland and in the Mpumalanga lowveld.ⁱⁱ A prevalence survey is currently being conducted amongst learners, which may provide more accurate and representative data regarding the distribution of soil-transmitted helminth infestation.^v

High prevalence of soil-transmitted helminth infestation has also been reported in urban areas, associated with poor sanitation.^{iv} The current Primary Health Care (PHC) Standard Treatment Guidelines (STGs) and Essential Medicines List (EML), 2014 edition recommends mebendazole,

oral for helmenthiasis (*Ascaris lumbricoides*; *Necator americanus*; *Enterobius vermicularis* and *Trichuris trichiura*).^{vi}

To assist with ensuring continuous availability of antihelminthic agents, a review of the published literature was undertaken to determine the comparable efficacy and safety of albendazole to mebendazole, oral in the South African setting.

5. Purpose/Objective

-P (*patient/population*): Adults and children ≥ 1 year of age

-I (*intervention*): Albendazole

-C (*comparator*): Mebendazole

-O (*outcome*): Eradication of soil-transmitted helminths; cure rates (CR) and egg reduction rates (ERR)

6. Methods:

a. **Data sources:** Cochrane Library, Google scholar.

b. **Search strategy:**

i. Cochrane library: Mesh term " *Ascaris* " resulted in retrieval of 2 systematic review and 72 trials.

ii. Google scholar search, using terms "albendazole, mebendazole, ascaris, trichurus, single dose, randomised controlled trial", since 2010 produced an additional RCT.

c. **Excluded studies:**

The following systematic review was excluded:

Author, date	Type of study	Reason for exclusion
Ziegelbauer K et al., 2012	Systematic review	Assessed the effect of sanitation on soil-transmitted helminth infestations.

Of the 72 trials retrieved from the Cochrane Library, 69 trials were excluded as these were not direct head-to-head comparisons of albendazole vs. mebendazole.

d. Evidence synthesis

Author, date	Type of study	n	Population	Comparators	Primary outcome	Effect sizes	Comments
Keiser et al., 2008	Systematic review	20 RCTs	Adults and children	Single-dose oral albendazole, mebendazole, and pyrantel pamoate agents individually compared to placebo	CR & ERR for <i>A. lumbricoides</i> ; <i>hookworm</i> and <i>T. trichiura</i> .	<p><i>A. lumbricoides</i> infection: -CR of 88% (95% CI, 79 to 93; $p < 0.01$, $n = 557$, $I^2 = 65.3$), 95% (91 to 97; $n = 309$), and 88% (79 to 93; $p < 0.001$; $I^2 = 0$, $n = 131$ patients), respectively.</p> <p>CR for hookworm infections: 72% (59 to 81; $p < 0.001$; $I^2 = 84.8$, $n = 742$), 15% (1 to 27; $p = 0.01$; $I^2 = 89.6$, $n = 853$), and 31% (19 to 42; $n = 152$), respectively.</p> <p>CR for <i>T. trichiura</i>: 28% (13 to 39; $p < 0.001$, $I^2 = 89.5$, $n = 735$), and 36% (16 to 51; $p = 0.001$; $I^2 = 94.5$, $n = 685$), respectively.</p> <p>Not all RCTs reported ERR, and ranges were provided.</p>	<p><i>Bias</i>: Quality of studies ranged from poor to moderate with Jadad score from 1 to 5 (studies underpowered, selection bias, measurement bias and publication bias present and studies were very heterogenous).</p> <p><i>Comparators</i>: All RCTs compared anthelmintic to placebo.</p> <p><i>Funding</i> by Swiss National Science Foundation and no financial disclosures reported.</p>
Lubis et al., 2012 ^{vii}	RCT	229	Primary school children (North West Indonesia)	Mebendazole 500 mg ($n = 106$) vs albendazole 400 mg ($n = 123$)	CR & ERR for <i>A. lumbricoides</i> ; <i>hookworm</i> and <i>T. trichiura</i> .	<p>Non-significant difference in CR 100% vs 96.7% and ERR of 100% vs 99.3% ($p > 0.05$).</p> <p><i>Secondary outcomes</i>: At week 4, embryonated eggs were higher in mebendazole vs albendazole groups (28.3% vs 13.8%; $p < 0.05$; NNT 7).</p>	<p>RCT with iTT analysis - method of randomisation or calculation of sample size not described.</p> <p><i>Selection bias & confounders</i>: Not determined as details of blinding & baseline patient</p>

							<p>demographics not provided.</p> <p><i>Measurement bias:</i> Blinding and inter-observer variances not described.</p> <p><i>Funding:</i> No external funding and no conflict of interests declared.</p>
Legesse et al., 2002 ^{viii}	RCT	468	Age 2 to 80 years (Wondo Genet, southern Ethiopia)	Mebendazole 100 mg 12 hourly x 3 days (n=200) vs. albendazole 400 mg (n=268)	CR and ERR of <i>A.lumbricoides</i> and <i>T. trichiura</i> .	<p><i>A. lumbricoides</i> CR & ERR comparable: 96% vs 99 %; p=0.062 & 99.8% vs 99.9%; p=0.0004; respectively</p> <p><i>T. trichiura</i> CR: 34.7% vs 13.9%; p <0.05, NNT 5</p> <p><i>T. trichiura</i> ERR: 92.3% vs 63.4%; p < 0.05, NNT 4</p> <p>More AEs reported with albendazole vs mebendazole</p>	<p>Cross-sectional survey.</p> <p>Study subjects randomised; blinding not reported.</p> <p><i>Funding:</i> Details of funding and conflicts of interests not disclosure.</p>
Steineman et al., 2011 ^{ix}	RCT	378	Children ≥ 5 years of age and adults (highly endemic region in People's Republic of China)	Albendazole 400 mg vs. mebendazole 500 mg vs albendazole 400mg x 3 days vs mebendazole 500 mg x 3 days.	CR against hookworm 3 to 4 weeks following dosing.	<p>Hookworm CR: 69.1% (55.2 to 80.9) vs 31.0% (19.5 to 44.5) vs 92.0% (80.8 to 97.8) vs 58.5% (45.6 to 70.6)</p> <p><i>Secondary outcomes:</i> - Hookworm ERR: 97 % vs 84% vs 99.7% vs 96%.</p> <p>- <i>A. lumbricoides</i> CR:</p>	<p><i>Selection bias:</i> Open-label, outcome-assessors blinded RCT.</p> <p><i>Attrition bias</i> - per protocol analysis (64 loss to follow up).</p>

						<p>96.1%(89.1 to 99.2) vs 93.0% (84.3 to 97.7) vs 96.8%(89.0 to 99.6) vs 93.1% (84.5 to 97.7)</p> <p>- <i>A. lumbricoides</i> ERR: All >99.9%</p> <p>- <i>T. trichiura</i> CR: 33.8%(22.6 to 46.6) vs 39.7%(27.6 to 52.8) vs 56.2% (41.2 to 70.5) vs 70.7%(57.3 to 81.9)</p> <p>- <i>T. trichiura</i> ERR: 76.7% (62.6 to 86.1) vs 82.5% (71.0 to 89.6) vs 94.0% (89.4 to 96.8) vs 97.3% (94.9 to 98.8)</p>	
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e. Evidence quality: The overall quality of RCTs was poor (see comments in the table above).

f. Conclusion:

Evidence suggests that albendazole is comparable to mebendazole for the eradication of *Ascaris lumbricoides*.

Furthermore, albendazole has been shown to be more efficacious than mebendazole for eradication of hookworm, whilst a three day course of mebendazole was shown to be the most efficacious treatment for *Trichuris trichiura*.

Safety data in infants ≥ 1 year of age is limited^x. "Available evidence indicates that albendazole and mebendazole may be used in children aged 12 months and older provided that the case for their use is established. The health benefits of treatment appear to override any risks associated with the correct administration of the drugs".^x

"In 1-year-old children, the World Health Organization recommends reducing the albendazole dose to half of that given to older children and adults for single-dose and 3-day treatment".^{xi}

Epidemiological considerations should guide recommendations for the local South African setting. Both benzimidazole agents have been shown to be efficacious against the most commonly reported helminth in South Africa, *Ascaris lumbricoides*

EVIDENCE TO DECISION FRAMEWORK

	JUDGEMENT	SUPPORTING EVIDENCE & ADDITIONAL CONSIDERATIONS									
QUALITY OF EVIDENCE	<p>What is the overall confidence in the evidence of effectiveness?</p> <p>Confident Not confident Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>										
BENEFITS & HARMS	<p>Do the desirable effects outweigh the undesirable effects?</p> <p>Benefits outweigh harms Harms outweigh benefits Benefits = harms or Uncertain</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>										
THERAPEUTIC INTERCHANGE	<p>Therapeutic alternatives available:</p> <p>Yes No</p> <p><input checked="" type="checkbox"/> <input type="checkbox"/></p> <p>- Albendazole and mebendazole</p> <p>Doses:</p> <table border="1"> <thead> <tr> <th></th> <th>Mebendazole</th> <th>Albendazole</th> </tr> </thead> <tbody> <tr> <td>Children 1-2 yrs</td> <td>100 mg 12 hrly x 3 days</td> <td>200 mg as a single dose</td> </tr> <tr> <td>Children ≥ 2 yrs & adults</td> <td>500 mg as a single dose</td> <td>400 mg as a single dose</td> </tr> </tbody> </table> <p>List specific exclusion from the group: n/a</p>		Mebendazole	Albendazole	Children 1-2 yrs	100 mg 12 hrly x 3 days	200 mg as a single dose	Children ≥ 2 yrs & adults	500 mg as a single dose	400 mg as a single dose	<p>Rationale for therapeutic alternatives included: Refer to rationale above.</p> <p>References: Refer to references below.</p> <p>Rationale for exclusion from the group: n/a References: n/a</p>
	Mebendazole	Albendazole									
Children 1-2 yrs	100 mg 12 hrly x 3 days	200 mg as a single dose									
Children ≥ 2 yrs & adults	500 mg as a single dose	400 mg as a single dose									
VALUES & PREFERENCES / ACCEPTABILITY	<p>Is there important uncertainty or variability about how much people value the options?</p> <p>Minor Major Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p> <p>Is the option acceptable to key stakeholders?</p> <p>Yes No Uncertain</p> <p><input type="checkbox"/> <input type="checkbox"/> <input type="checkbox"/></p>	<p><u>Patient compliance:</u> Albendazole may be administered as a single dose in both children and adults. Mebendazole may only be administered as a single dose in adults and children > 2 years of age.</p>									

RESOURCE USE	How large are the resource requirements? More intensive <input type="checkbox"/> Less intensive <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/>	Cost of medicines/treatment course: <table border="1"> <thead> <tr> <th>Medicine</th> <th>Average weighted price (ZAR)</th> </tr> </thead> <tbody> <tr> <td colspan="2">CHILDREN: 1-2 years</td> </tr> <tr> <td>Mebendazole, 100 mg tab (6)</td> <td>R 3.99*</td> </tr> <tr> <td>Albendazole, 200 mg tab (1)</td> <td>R 7.94**</td> </tr> <tr> <td colspan="2">CHILDREN ≥ 2 years and ADULTS</td> </tr> <tr> <td>Mebendazole, 500 mg tab (1)</td> <td>R 3.64*</td> </tr> <tr> <td>Albendazole, 400 mg tab (1)</td> <td>R 4.43*</td> </tr> </tbody> </table> <small>*Current contract circular, HP02-2015AI/02 **60 % of price listed on SEP Database 17 February 2017 (R13.24)</small> Additional resources: n/a	Medicine	Average weighted price (ZAR)	CHILDREN: 1-2 years		Mebendazole, 100 mg tab (6)	R 3.99*	Albendazole, 200 mg tab (1)	R 7.94**	CHILDREN ≥ 2 years and ADULTS		Mebendazole, 500 mg tab (1)	R 3.64*	Albendazole, 400 mg tab (1)	R 4.43*
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Albendazole, 400 mg tab (1)	R 4.43*															
EQUITY	Would there be an impact on health inequity? Yes <input type="checkbox"/> No <input checked="" type="checkbox"/> Uncertain <input type="checkbox"/>															
	Is the implementation of this recommendation feasible? Yes <input checked="" type="checkbox"/> No <input type="checkbox"/> Uncertain <input type="checkbox"/>															

Type of recommendation	We recommend against the option and for the alternative <input type="checkbox"/>	We suggest not to use the option or to use the alternative <input type="checkbox"/>	We suggest using either the option or the alternative <input type="checkbox"/>	We suggest using the option <input type="checkbox"/>	We recommend the option <input checked="" type="checkbox"/>
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Recommendation: Base on this evidence review the PHC Committee recommend albendazole or mebendazole for soil-transmitted helminths in adults and children at primary level of care.

Rationale: Evidence of comparable efficacy of mebendazole and albendazole for eradication of *Ascaris lumbricoides*, currently the most common soil-transmitted helminth in South Africa. In addition, the available evidence indicates that albendazole and mebendazole may be used in children aged 12 months and older provided that the case for their use is established. The health benefits of treatment appear to override any risks associated with the correct administration of these antihelminthic agents.

Level of Evidence: II low-moderate quality RCT

Review indicator:Evidence
of efficacyEvidence of
harmPrice
reduction**VEN status:**

Vital

Essential

Necessary

Monitoring and evaluation considerations

Research priorities

More widespread local prevalence studies/surveys to guide treatment going forward.

National Department of Health: Affordable Medicines - Essential Drugs Programme in collaboration with Cochrane South Africa, South African Medical Research Council

Medicine review/motivation form template: October 2016_v5.0

ⁱ Jinabhai CC, Taylor M, Coutsooudis A, Coovadia HM, Tomkins AM, Sullivan KR. Epidemiology of helminth infections: implications for parasite control programmes, a South African perspective. *Public Health Nutr.* 2001 Dec;4(6):1211-9. <https://www.ncbi.nlm.nih.gov/pubmed/11796084>

ⁱⁱ Mabaso ML, Appleton CC, Hughes JC, Gouws E. Hookworm (*Necator americanus*) transmission in inland areas of sandy soils in KwaZulu-Natal, South Africa. *Trop Med Int Health.* 2004 Apr;9(4):471-6. <https://www.ncbi.nlm.nih.gov/pubmed/15078265>

ⁱⁱⁱ Appleton CC, Mosala TI, Levin J, Olsen A. Geohelminth infection and re-infection after chemotherapy among slum-dwelling children in Durban, South Africa. *Ann Trop Med Parasitol.* 2009 Apr;103(3):249-61. <https://www.ncbi.nlm.nih.gov/pubmed/19341539>

^{iv} Adams VJ, Markus MB, Adams JF, Jordaan E, Curtis B, Dhansay MA, Obihara CC, Fincham JE. Paradoxical helminthiasis and giardiasis in Cape Town, South Africa: epidemiology and control. *Afr Health Sci.* 2005 Sep;5(3):276-80. <https://www.ncbi.nlm.nih.gov/pubmed/16246001>

^v Communication from NDoH Child and Youth Health Directorate.

^{vi} PHC STGs and EML, 2014.

^{vii} Lubis IN, Pasaribu S, Lubis CP. Current status of the efficacy and effectiveness of albendazole and mebendazole for the treatment of *Ascaris lumbricoides* in North-Western Indonesia. *Asian Pac J Trop Med.* 2012 Aug;5(8):605-9. <https://www.ncbi.nlm.nih.gov/pubmed/22840447>

^{viii} Legesse M, Erko B, Medhin G. Efficacy of albendazole and mebendazole in the treatment of *Ascaris* and *Trichuris* infections. *Ethiop Med J.* 2002 Oct;40(4):335-43.

^{ix} Steinmann P, Utzinger J, Du ZW, Jiang JY, Chen JX, Hattendorf J, Zhou H, Zhou XN. Efficacy of single-dose and triple-dose albendazole and mebendazole against soil-transmitted helminths and *Taenia* spp.: a randomized controlled trial. *PLoS One.* 2011;6(9):e25003. <https://www.ncbi.nlm.nih.gov/pubmed/21980373>

^x Montresor A, Awasthi S, Crompton DW. Use of benzimidazoles in children younger than 24 months for the treatment of soil-transmitted helminthiasis. *Acta Trop.* 2003 May;86(2-3):223-32. <https://www.ncbi.nlm.nih.gov/pubmed/12745139>

^{xi} American Academy of Pediatrics. In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Diseases.* Elk Grove Village, IL: American Academy of Pediatrics; 2012:241. https://redbook.solutions.aap.org/DocumentLibrary/RB12_interior.pdf