(1) Have all important studies that you are aware of been included?
   Yes  X  No  

(2) Is there adequate evidence of efficacy for the proposed use?
   Yes  
   No  X

(3) Is there evidence of efficacy in diverse settings and/or populations?
   Yes  X  No  

(4) Are there adverse effects of concern?
   Yes  
   No  X

(5) Are there special requirements or training needed for safe/effective use?
   Yes  
   No  X

(6) Is this product needed to meet the majority health needs of the population?
   Yes  X  No  

(7) Is the proposed dosage form registered by a stringent regulatory authority?
   Yes  X  No  

(8) What action do you propose for the Committee to take?
   **For 6.1.1 Intestinal anthelminthics**
   Based on the evidence provided by the current review I propose retaining albendazole, mebendazole, praziquantel, and pyrantel, adding ivermectin, and discussing the deletion of levamisole and niclosamide.

   **For 6.1.2 Antifilarials**
   Based on the evidence provided by the current review I propose retaining ivermectin and diethylcarbamazine, and adding albendazole for combination therapy.

   **For 6.1.3 Antischistosomals and antitrematode medicines**
   Based on the evidence provided by the current review I propose retaining praziquantel and triclabendazole, and considering the deletion of oxamniquine for children.
For 6.5.1 Antiamoebic and antigiardiasis medicines
Based on the evidence provided by the current review I propose retaining metronidazole and diloxanide.

For 6.5.5.1 African trypanosomiasis
Based on the evidence provided by the current review I propose retaining pentamidine and eflornithine and deleting suramin and melarsoprol for children.

For 6.5.5.2 American trypanosomiasis
Based on the evidence provided by the current review I propose retaining benznidazole, and deleting nifurtimox for children at this moment.

(9) Additional comment, if any.

Neglected tropical diseases (NTDs) are a group of communicable diseases which thrive in impoverished settings and blight the lives of around one billion people worldwide, while threatening the health of millions more. There are currently 149 countries and territories where neglected tropical diseases are endemic, at least 100 of which are endemic for 2 or more of these diseases, and 30 countries that are endemic for 6 or more. In the available review the diseases identified as the main NTDs are: dengue, rabies, trachoma, buruli ulcer, endemic treponematoses (including yaws), leprosy, Chagas disease (American trypanosomiasis), human African trypanosomiasis (sleeping sickness), leishmaniasis, cysticercosis, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematode infections, lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), schistosomiasis (bilharziasis), and soil-transmitted helminthiases (intestinal parasitic worms). The review analysed medicines which treat or control helminthic infections and some of the protozoal infections.1

HELMINTH INFECTIONS
Among the NTD the review includes cysticercosis, dracunculiasis (guinea-worm disease), echinococcosis, foodborne trematode infections, lymphatic filariasis (elephantiasis), onchocerciasis (river blindness), schistosomiasis (bilharziasis), soil-transmitted helminthiases (intestinal parasitic worms). Table 1 includes the recommended medicines for the treatment of these helminthic infections.2
Table 1. Helminth infections and recommended anthelmintics *

<table>
<thead>
<tr>
<th>Diseases</th>
<th>Parasites</th>
<th>1st choice</th>
<th>2nd choice</th>
</tr>
</thead>
<tbody>
<tr>
<td>Soil-transmitted helminthiases</td>
<td><em>Ancylostoma duodenale</em></td>
<td>albendazole,</td>
<td>pyrantel</td>
</tr>
<tr>
<td>(hookworms)</td>
<td><em>Necator americanus</em></td>
<td>mebendazole</td>
<td></td>
</tr>
<tr>
<td>Ascariasis</td>
<td><em>Ascaris lumbricoides</em></td>
<td>mebendazole,</td>
<td>pyrantel</td>
</tr>
<tr>
<td>(roundworm)</td>
<td></td>
<td>albendazole</td>
<td></td>
</tr>
<tr>
<td>Trichuriasis</td>
<td><em>Trichuris trichiura</em></td>
<td>mebendazole,</td>
<td>albendazole</td>
</tr>
<tr>
<td>(whipworm)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Strongyloidiasis</td>
<td><em>Strongyloides stercoralis</em></td>
<td>ivermectin</td>
<td>thiabendazole,</td>
</tr>
<tr>
<td>(threadworm)</td>
<td></td>
<td></td>
<td>diethylcarbamazine</td>
</tr>
<tr>
<td>Lymphatic filariasis</td>
<td><em>Wuchereria bancrofti</em>,</td>
<td>albendazole,</td>
<td></td>
</tr>
<tr>
<td>(elephantiasis)</td>
<td><em>Brugia malay</em></td>
<td>ivermectin</td>
<td></td>
</tr>
<tr>
<td>Onchocerciasis (river blindness)</td>
<td><em>Onchocerca volvulus</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobiasis</td>
<td><em>Enterobius vermicularis</em></td>
<td>albendazole,</td>
<td>pyrantel</td>
</tr>
<tr>
<td>(pinworm)</td>
<td></td>
<td>mebendazole</td>
<td></td>
</tr>
<tr>
<td>Dracunculiasis (guinea-worm disease)</td>
<td><em>Dracunculus medinensis</em></td>
<td></td>
<td>metronidazole</td>
</tr>
<tr>
<td>Echinococcosis (hydatid disease)</td>
<td><em>Echinococcus sp.</em></td>
<td>albendazole</td>
<td>praziquantel</td>
</tr>
<tr>
<td>Taeniasis</td>
<td><em>Taenia saginata</em> (beef</td>
<td>praziquantel</td>
<td>niclosamide</td>
</tr>
<tr>
<td>tapeworm)</td>
<td><em>Taenia solium</em> (pork</td>
<td></td>
<td></td>
</tr>
<tr>
<td>tapeworm)</td>
<td><em>Schistosoma mansoni</em>,</td>
<td>albendazole</td>
<td>praziquantel</td>
</tr>
<tr>
<td>Neurocysticercosis</td>
<td><em>S. haematobium</em>, *S.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(bilharziasis)</td>
<td><em>japonicum</em></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foodborne trematode infections</td>
<td><em>Paragonimus sp.</em>, <em>Opisthorchis sp.</em>, <em>Clonorchis sinensis</em></td>
<td>praziquantel</td>
<td></td>
</tr>
<tr>
<td>Fascioliasis</td>
<td><em>Fasciola hepatica</em></td>
<td>triclabendazole</td>
<td></td>
</tr>
</tbody>
</table>

* Adapted from the reference 2.

Based on the evidence reported in the previous review, I suggest the section 6.1 of the WHO Model List of Essential Medicines for Children 2nd List (updated) March could include the following anthelmintics.

6.1 Anthelminthics

6.1.1 Intestinal anthelmintics

albendazole Tablet (chewable): 400 mg.
In a meta-analysis involving studies performed in adults and children, a single-dose oral albendazole (400 mg) appears to be superior to a single-dose oral mebendazole, levamisole and pyrantel pamoate against hookworm infections, although few studies
compared the drugs head-to-head. Albendazole was associated with cure rates of 88%, 72% and 28% for ascariasis, hookworm infections and trichuriasis, respectively. In the 11 studies included in this meta-analysis albendazole was well tolerated. For the treatment of cystic hydatid disease albendazole is considered the first choice. Albendazole is also the preferred treatment of neurocysticercosis.

A meta-analysis of six trials which randomly assigned 464 patients with cystic lesions (vesicular cysticerci) and 5 trials which randomly assigned 478 patients with enhancing lesions (colloidal cysticerci) showed that the cysticidal drug therapy (albendazole and praziquantel) results in complete resolution of colloidal and vesicular cysticerci, lower risk for recurrence of seizures in patients with colloidal cysticerci, and a 67% reduction in the rate of generalized seizures with the treatment. Another meta-analysis (six prospective studies, only two RCTs) compared albendazole with praziquantel in patients with vesicular cysticerci and showed the superiority of albendazole in the control of seizures and in the total disappearance of cysts. There was no difference between albendazole and praziquantel in proportion of patients with adverse events, and development of intracranial hypertension, due to the administered therapy.

A recent Cochrane review found no trials for viable lesions in children. For viable lesions in adults, no difference was detected for albendazole compared with no treatment for recurrence of seizures; but fewer participants with albendazole had lesions at follow-up. For non-viable lesions in children, seizures recurrence was less common with albendazole compared with no treatment. There was no difference detected in the persistence of lesions at follow-up (570 participants, six trials). For non-viable lesions in adults, there were no trials. In trials including viable, non-viable or mixed lesions (in both children and adults), headaches were more common with albendazole alone, but no difference was detected in one trial giving albendazole with corticosteroids (116 participants, one trial).

A prospective, interventional, randomized, placebo-controlled, double-blind clinical trial (n=103 children with seizures for <3 months and single lesion neurocysticercosis) evaluated albendazole (15 mg/kg/d) administered for 7 days with either praziquantel (75 mg/kg/day; n=53) or placebo (n=53) for 1 day according to random allocation. All children were followed up for at least 6 months. A combination therapy for albendazole and praziquantel was statistically comparable to sole therapy with albendazole in eradicating lesions and preventing seizures. A randomized, placebo-controlled, double blind clinical trial compared efficacy of 1 and 4 weeks of albendazole therapy in 122 children with neurocysticercosis. All children received albendazole (15 mg/kg/day) for 7 days followed by either albendazole or placebo for the following 21 days according to their random number allocation. All children were followed for at least 2 years. Complete resolution of lesions was similar in the two therapy groups on the first (42% vs. 39%) and second (77% vs. 79%) follow-ups. Reduction in total number and size was also similar. Also the proportion of lesions that calcified (5% vs. 10%) did not differ significantly. Seizure control at 2 years was similar in the 2 groups.

**levamisole**

Table: 50 mg; 150 mg (as hydrochloride)

A meta-analysis evaluating the efficacy of current medicines against soil-transmitted helminth infections did not identify a single RCT related to levamisole efficacy. Two
placebo-controlled were found, but none was randomised. For ascariasis, the overall cure rate of 91.5% was obtained with a single oral dose of 80 mg or 2.5 mg/kg. The meat-analysis found only 1 randomized placebo-controlled trial performed in children infected with *T. trichiura* who received either 40 or 80 mg levamisole (LVM) and attained a low cure rate (9.6%) and a low egg reduction rate (41.5%). The overall cure rate of 2 non-randomized placebo-controlled trials was 8.6%.

For the treatment of hookworm infection, one randomized placebo-controlled trial carried out in Tanzania and another one in Malawi, administering levamisole at 40 or 80 mg (equivalent to 1.25-2.5 mg/kg), depending on the individual's weight or age, achieved cure rates of 11.9% and 10%, respectively. In comparison to mebendazole (MBZ) or the combination MBZ/LVM, LVM alone had a smaller effect on egg clearance. The calculated overall cure rate was 38.2% in 4 non–randomized placebo-controlled trials. So, levamisole presents a good efficacy in parasitological cure of *Ascaris lumbricoides* infections, but inferior comparative efficacy in hookworm and *T. trichiura* infections.

**Suggestion:** To discuss levamisole deletion due to scarce evidence of efficacy, and to an inferior parasitological cure rate for hookworm infection and trichuriasis in comparison to albendazole, mebendazole or pyrantel pamoate.

**mebendazole**
Tablet (chewable): 100 mg; 500 mg.

**niclosamide**
Tablet (chewable): 500 mg.

Niclosamide was listed for use when praziquantel treatment fails. No studies were identified that met the inclusion criteria in the previous review. It is a second option in the treatment of *T. saginata*, *Diphyllobothrium latum*, *Hymenolepis nana* and other cestodes. Niclosamide is still used because it is cheap, effective and available in many parts of the world. It is as effective and safe as praziquantel, but, if the parasitological diagnosis is uncertain, praziquantel is the preferred medicine because of the danger of cysticercosis to people infected with *T. solium*, because ova released from drug-damage gravid worms develop into larvae that can cause cysticercosis, a dangerous infection. It is no longer approved in USA. The current review did not find evidence about the use of niclosamide in children.

**Suggestion:** To discuss niclosamide deletion due to the lack of evidence in children, the higher efficacy of praziquantel in *T. saginata* infection, the almost exclusive benefit of niclosamide in this condition, and the potential risk in people infected with *Taenia solium*.

**praziquantel**
Tablet: 150 mg; 600 mg.

**pyrantel**
Oral liquid: 50 mg (as embonate)/ml
Tablet (chewable): 250 mg (as embonate).

**ivermectin**
Tablet (scored): 3 mg; 6 mg.

Ivermectin is considered the best anthelmintic for treating intestinal strongiloidiasis. Thiabendazole shows efficacy comparable to that of ivermectin but is far more toxic. Information on the best treatment for disseminated disease and hyperinfection is
limited. Hyperinfection may require prolonged or repeated therapy. Albendazole is an alternative, but with lesser efficacy.  

6.1.2 Antifilarials

Ivermectin Tablet (scored): 3 mg; 6 mg.

Albendazole Albendazole (ALB) has been combined with either diethylcarbamazine (DEC) or ivermectin (IVM) for treating lymphatic filariasis. However, there is insufficient evidence to confirm or refute this strategy. Albendazole combined with ivermectin appears to have a small effect on microfilaraemia, but this was not consistently demonstrated. On the other hand, a systematic review reported a significant reduction in macrofilaricidal and microfilaricidal effect in the combined regime of DEC and ALB compared to DEC alone. IVM is usually administered in combination with ALB. Two studies have shown that this combination is more effective in killing microfilaria in humans and reducing infection rates in the vector than individual agents or placebo. ALB and DEC are used as a combination for mass drug administration (MDA) in many nononchocerciasis-endemic populations, and has been proven to be effective. The main cause for concern, however, is resistance to ALB which could be seen in nematode infections during the large scale and prolonged exposure to ALB during MDA. This could pose a serious threat to health of children and adults in endemic areas.

<table>
<thead>
<tr>
<th>Suggestion: To discuss the inclusion of albendazole to be used in combination with diethylcarbamazine or ivermectin.</th>
</tr>
</thead>
</table>

Diethylcarbamazine Tablet: 50 mg; 100 mg (dihydrogen citrate). The expert committee has suggested this medicine be reviewed for possible deletion. Diethylcarbamazine (DEC) remains the prime antifilarial agent with a well-established microfilaricidal and some macrofilaricidal effects. The macrofilaricidal action of DEC is not intended to reverse existing lymphatic damage but prevent further adult worm associated lymphatic damage and dysfunction. The best results are achieved in W. bancrofti and B. malay if chemotherapy is started early, before the obstruction has occurred. Ivermectin (IVM) is highly microfilaricidal but minimally macrofilaricidal. The role of albendazole (ALB) in treatment regimens is not well established though the drug has a microfilaricidal effect. However, the combination of DEC+ALB has a better long-term impact than IVM+ALB. DEC is partially effective against onchocerciasis, but induces serious reactions. For this reason, ivermectin has replaced diethylcarbamazine for therapy of onchocerciasis. The use of diethylcarbamazine is avoided in areas where onchocerciasis is endemic. Pretreatment with corticosteroids is often undertaken to minimize indirect reactions to diethylcarbamazine that result from dying microfilariae. Current studies have indicated that single-dose treatment with 6 mg/kg DEC has comparable macrofilaricidal and long-term microfilaricidal efficacy as the 12-day course of DEC. Single-dose treatment can be repeated every 6–12 months for persons
who remain infected. This regimen presents benefits concerning cost, convenience, and patient compliance.
A community-based trial on head to head comparison on the efficacy of DEC (6 mg/kg, single dose) and IVM (400 μg/kg, single dose) in South India has shown that after 10 years of annual MDA, DEC had the potential to interrupt the transmission of filariasis while IVM was less able to do so. DEC used alone for mass drug administration in Fiji has also shown a statistically significant reduction in microfilaria rates. 

Suggestion: To maintain diethylcarbamazine and switch it from the complementary to the core list.

6.1.3 Antischistosomals and antitrematode medicines

praziquantel  
Table: 600 mg.

triclabendazole  
Table: 250 mg.

oxamniquine  
Capsule: 250 mg. Oral liquid: 250 mg/5 ml.

Oxamniquine is listed for use when praziquantel treatment fails. It is a second choice medicine to praziquantel for the treatment of schistosomiasis caused by S. mansoni. It continues to be used in South America due to high efficacy after a single oral dose, low incidence of mild side effects, and low price. A Cochrane review included 13 randomised and quasi-randomised trials comparing oxamniquine and/or praziquantel with placebo for the treatment of S. mansoni. In Brazil, 15 to 19 mg/kg oxamniquine is as effective as 50 to 70 mg/kg praziquantel in people older than 14 years (OR = 0.61; 95% CI: 0.26 to 1.46). In Africa, 15 mg/kg oxamniquine is less effective than 40 mg/kg praziquantel in people older than 14 years (OR= 0.23; 95% CI: 0.09 to 0.60), but no difference was shown using 30 mg/kg oxamniquine (OR=2.88; 95% CI: 0.69 to 11.96). Both drugs appear safe.

The current review pointed that lower doses in children are not as successful in achieving cure as the same doses in adults. Higher doses are associated with an increase in adverse events. Oxamniquine appears to be better tolerated and more effective in adults.

Suggestion: To consider the deletion of oxamniquine for children, due to its lesser effectiveness and tolerability in comparison to adults.

PROTOZOAL INFECTIONS

Among the NTD this review considered the following protozoal infections: Chagas disease (American trypanosomiasis), human African trypanosomiasis (sleeping sickness), leishmaniasis, amoebiasis, giardiasis, trichomoniasis, toxoplasmosis, cryptosporidiosis, malaria.

Based on the evidence reported in the current review, I suggest the section 6.5 of the WHO Model List of Essential Medicines for Children 2nd List (updated) March could include the following antiprotozoal medicines.
6.5 Antiprotozoal medicines
6.5.1 Antiamoebic and antigiardiasis medicines
diloxanide Tablet: 500 mg (furoate) a >25 kg.

metronidazole Oral liquid: 200 mg (as benzoate)/5 ml. Tablet: 200 mg to 500 mg.

In the updated (2010) WHO Essential Medicines List for Children, the former Expert Committee required a review of diloxanide effectiveness and safety for amoebiasis, with emphasis on comparative efficacy, safety, and age limits compared with oral paromomycin. According to the current review the evidence is scarce (one comparative trial; n=39) and unable to determine efficacy data. The retrospective analysis reported 86% of parasitological cure rate and accepted safety, especially for persons aged 20 months to 10 years.

6.5.5 Antitrypanosomal medicines
6.5.5.1 African trypanosomiasis
pentamidine Powder for injection: 200 mg (pentamidine isetionate) in vial. To be used for the treatment of Trypanosoma brucei gambiense infection.
suramin sodium Powder for injection: 1 g in vial. To be used for the treatment of the initial phase of Trypanosoma brucei rhodesiense infection.

No studies from which paediatric data could be extracted were found. So, I suggest not including suramin sodium in the list for children.

Medicines for the treatment of 2nd stage African trypanosomiasis
eflornithine Injection: 200 mg (hydrochloride)/ml in 100-ml bottle. To be used for the treatment of Trypanosoma brucei gambiense infection.
melarsoprol Injection: 3.6% solution in 5-ml ampoule (180 mg of active compound).

According to the current review eflornithine is an effective treatment and much safer than melarsoprol. A randomized, open-label, active control, parallel clinical trial performed in 54 stage 2-patients compared three medicine combinations: melarsoprol-nifurtimox (M+N), melarsoprol-eflornithine (M+E), and nifurtimox-eflornithine (N+E). The last combination provided significantly higher cure rates. Adverse events were less frequent and less severe with N+E, resulting in fewer treatment interruptions and no fatalities. Larger studies are needed to continue the evaluation of this drug combination in the treatment of T. brucei gambiense sleeping sickness.

In 2009, a multicentre, randomised, open-label, active control, phase III, non-inferiority trial identified that the efficacy of nifurtimox-eflornithine combination therapy (NECT) is non-inferior to that of eflornithine monotherapy. This study was performed in patients with 15 years or older and confirmed second-stage T. brucei...
 gambiense infection. The combination treatment also presented safety advantages, although adverse side effects were frequent in both groups. At this moment, nifurtimox is not recommended for inclusion in the List because there is not evidence of efficacy and safety in people under 15 years old.

Melarsoprol is poorly tolerated by all age groups, with the very young (<2 years) being prone to jaundice and rash more commonly than the adults treated. In pre-school age children, there is a lower incidence of encephalopathic syndrome, but those who did develop it had a higher mortality rate. All studies found melarsoprol to be significantly toxic, with some deaths attributable to adverse effects of the treatment. Eflornithine monotherapy and NECT are likely to replace melarsoprol, with careful parasite resistance monitoring.  

<table>
<thead>
<tr>
<th>Suggestion: To delete melarsoprol due to its association with relevant side effects in children, especially the very young.</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5.5.2 American trypanosomiasis</td>
</tr>
<tr>
<td>benznidazole</td>
</tr>
<tr>
<td>nifurtimox</td>
</tr>
</tbody>
</table>

A systematic review (3 clinical trials and 6 observational studies) 17 showed that benznidazole increases 18-fold the probability of a response to therapy (OR= 18.8; 95% CI: 5.2-68.30 in comparison to placebo or no treatment. This effect was mainly observed in clinical trials. Patients treated with benznidazole had a significantly lower risk of clinical events (OR=0.29; 95% CI: 0.16-0.53). Up to 18% of patients discontinued treatment due to toxicity (cutaneous reactions followed by gastrointestinal disturbances); this was less common in children than in adults. A Cochrane review18 included two old studies performed in children. In the first, a randomised, double-blind, placebo-controlled trial performed with 130 schoolchildren (aged 7-12 years) in a rural area of Brazil with endemic Chagas disease, benznidazole (7.5 mg/kg daily for 60 days by mouth) evidenced to be safe and 55.8% effective in producing negative seroconversion of specific antibodies. 19 Another double-blind, randomised, clinical field trial tested the efficacy and tolerance of benznidazole (5 mg/kg/day for 60 days) for treating children (six to 12 years old) in the indeterminate phase of infection by Trypanosoma cruzi. After a four year follow-up, 62% of the benznidazole-treated children and no placebo-treated child were seronegative for T. cruzi. 20 An Argentinean prospective cohort study21 of 107 infants and children (mean age: 6.9 years) with asymptomatic Chagas disease evaluated the treatment with benznidazole. Sixty-two adverse events (in 44 children) were considered benznidazole related. The adverse reactions occurred in children older than 7 years. The adverse reaction rate was lower in infants and toddlers compared with older children (18% vs. 53%) (P < 0.001). Most reactions were mild and did not require treatment suspension. In conclusion, treatment with benznidazole was well tolerated in children.
No studies were found describing the use of nifurtimox in the treatment of American trypanosomiasis in children.

An Argentinean review stated both benznidazole and nifurtimox have been shown to be effective in the treatment of both acute and early chronic phases in children, but the pharmacokinetics of these drugs have never been studied in this population.

Suggestion: To retain benznidazole and to delete nifurtimox for the treatment of American trypanosomiasis in children.

References

