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ภิรมย์ กมลรัตนกุล : ความสัมพันธ์ระหว่างการติดเชื้อพยาธิไส้เดือนและภาวะทุพโภชนาการ จุฬาลงกรณ์เวชสาร 2527 กุมภาพันธ์ ; 28 (2) : 189-204

จากการวิเคราะห์รายงานต่าง ๆ เพื่อหาข้อสรุปเกี่ยวกับความสัมพันธ์ระหว่างการติดเชื้อพยาธิไส้เดือนและภาวะทุพโภชนาการในเด็ก ยังไม่สามารถยืนยันได้แน่นอนว่า การติดเชื้อพยาธิไส้เดือนเป็นสาเหตุหนึ่งของภาวะทุพโภชนาการหรือไม่ อย่างไรก็ตาม ความสัมพันธ์นี้มีแนวโน้มจะเป็นจริงในเด็กที่มีการติดเชื้อพยาธิไส้เดือนอย่างรุนแรงร่วมกับมีภาวะทุพโภชนาการร่วมด้วย

ในทำนองเดียวกัน จากการวิเคราะห์รายงานที่ศึกษาถึงผลของการให้ยาถ่ายพยาธิไส้เดือนในเด็กต่อการเปลี่ยนแปลงในทางที่ดีขึ้นของภาวะโภชนาการก็ยังหาข้อสรุปไม่ได้เช่นกัน ดังนั้นการศึกษาอย่างจริงจังถึงเรื่องนี้โดยออกแบบการศึกษาที่เหมาะสมจึงเป็นเรื่องที่น่าสนใจเป็นอย่างยิ่งสำหรับประเทศไทย ซึ่งพบอุบัติการของการติดเชื้อพยาธิไส้เดือนและภาวะทุพโภชนาการสูงในเด็ก

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I. Introduction

Our knowledge of the interaction of malnutrition and Ascaris infection is still poorly developed. Although ascariasis is very common, affecting perhaps one-fourth of the humanity,[1,2] the importance of its effect on nutrition in human has been inadequately studied.

The role of ascariasis as a contributory factor of the etiology of childhood malnutrition has often been illustrated by clinical observation in patients with massive infection[3,4,5,6,7,8] whereas more systematic evidence is scarce and mainly based on small hospital materials presenting contradictory results. Clinical experience as well as some metabolic studies indicated that massive infection with ascariasis may result in malnutrition. Community based studies[9,10,11,12,13] reporting on the gross relationship between ascariasis and nutritional status of children are seemingly few.

II. Studies in Animals

The adverse effect of massive ascaris infection on host nutrition in experimental animals is well documented.[14,15]

Nesheim et al studied the influence of Ascaris suum infection in malnourished pigs and found that Ascaris infected pigs showed significantly lower nitrogen digestibility compared to uninfected controls. Fat absorption, lactose tolerance, and mucosal lactase activity were also lower in the infected. These studies suggested that Ascaris infection may cause nutrient losses in infected hosts.

Trends indicating decreased absorption of protein and fat and abnormalities of the small intestinal mucosa and tunica muscularis in malnourished Ascaris infected piglets have also been reported by Stephensons et al.[15] Controlled trials of antihelminthics in Ascaris infected chicks have shown more rapid weight gain in treated animals.

III. A Review of the Literature on Causation

The review of the literatures that claim to show causation will be based upon "*the principle of common sense*"[16] that involved two steps:

Step one : Deciding whether the basic methods used were strong or weak. A search for the studies documented in the medical literatures, no strong basic method used to determine the effect of ascariasis on the overall nutritional status of the human host, Most studies based on descriptive designs without formal control group. Such comparison are fraught with risk of drawing incorrect conclusion. There were a few cross-sectional survey[9,12,13]; however, this design is limited by the fact that in an Ascaris-endemic community, there may be frequent movement from infected to non-infected state and vice versa.[17] Thus, whereas

no stronger evidence is available, we are forced to discuss this issue based on such studies.

Step two : Applying the diagnostic tests for causation (see Table 1)

3.1 Is there evidence from true experiments in human? Although the true experiment (randomized trial) gives us the most accurate (or valid) answer to a question of causation, and therefore represents the strongest method, as already stated, we cannot find them in our clinical reading. Therefore, further research in this area is needed.

3.2 Is the association strong? In cross-sectional survey in the U.S., it has been reported that the mean weight-for-height index is lower in children with Ascaris infection than non-infected controls.[11,18] No cause-and-effect conclusion; however, can be drawn from these single point observation. *Blumenthal and Schultz*[9] found that 30 Ascaris-infected children significantly associated with low serum albumin and plasma ascorbic acid levels and was weakly associated with low weight-for-height and signs of riboflavin deficiency when compared with 30 uninfected matched controls.

3.3 Is the association consistent from study to study? Numerous field and hospital studies have investigated the possibilities that ascariasis plays a causal role in malnutrition. However, those studies have not yeilded consistent association. Some studies examine the effects of deworming of children under matabolic ward condition and have consistently demonstrated *impaired absorption of protein,*[4,6,7,8] *fat,*[4,6,7] and *d-xylose*[4,6] in the host under conditions where the *parasite load is heavy* and *the diet marginal.*

Similarly, the consistent finding of an adverse effect of ascariasis in infected children on *ascorbic acid absorption*[18,19,20] and *vitamin A absorption*[5,20] had also been reported.

Table 1 Step two : Applying the diagnostic tests for causation*

1. Is there evidence from true experiments in human?
2. Is the association strong?
3. Is the association consistent from study to study?
4. Is the temporal relationship correct?
5. Is there a dose-response gradient?
6. Does the association make epidemiologic sense?
7. Does the association make biological sense?
8. Is the association specific?
9. Is the association analogous to a previous proven causal association?

*Listed in decreasing order of importance

The findings reported by many *field studies*, on the other hand, have frequently proven ambiguous. While some studies have shown significant improvement in nutritional status after single[21] or periodic[22,23] episode of treatment for ascariasis, others have revealed no significant at all.[19,24,25,26]

3.4 Is the temporal relationship correct? As stated before, our knowledge of the interaction of nutrition and parasitism is still poorly developed. According to the concepts elaborated by *Scrimshaw et al*[27], these relationship are frequently *synergistic*, that is, mutually reinforcing. Impaired nutrition tends to decrease resistance to parasitic infection or its consequences and parasitism, in turn, impairs the nutritional status of the host. The simultaneous presence of both malnutrition and Ascaris infection will result in an interaction with consequences for the host more serious than the additive effect of the two working independently. Ascaris infection make malnutrition worse and poor nutrition increase the severity of infectious disease.[28]

3.5 Is there a dose-response gradient? The results from many studies suggested that an adverse effect of Ascaris infection on nutritional status were more pronounced among the moderately and heavily infected children than lightly infected or non-infected children.[9,29]

There appears to be little doubt that heavy and moderately heavy Ascaris infections constitute a continuing drain upon the host's supply of nutrients, particularly protein and vitamins, and that this is related to chronic undernutrition in young children. This drain is particularly important in those whose nutritional demands are greatest.

3.6 Does the association make epidemiologic sense? So far, there is a little clear-cut epidemiological information regarding the relative importance of ascariasis in the causation of malnutrition in countries suffering from concomitant infection.[3-13,18,20,30,31]

3.7 Does the association make biological sense? Several mechanisms exist whereby ascariasis may cause malnutrition :

3.7.1 The parasites may *suppress appetite* of the host.

3.7.2 The parasites may actually *ingest and metabolize nutrients* eaten by their host by direct digestion of food into their intestinal canal or absorption through the round-worm's intack skin.[32] Considerable quantities of barium meal and animal charcoal fed to subjects harbouring ascaris have been found in the bodies of the parasites. Ascaris demands high nutrition. This is indicated by its growth from a microscopic 2 mm. on first reaching the intestine to a length of 15 to 35 cm or more after only 8 to 10 weeks.[32]

3.7.3 They may cause nutrient loss *through the production of their*

ova[8]. It has been estimated that one female lays some 200,000 ova daily. This means that if a large numbers of worms are present, this represents yet another small, but significant nutrient loss[32].

3.7.4 The parasites may cause *incomplete digestion* and *malabsorption of nutrients* through some disruption of normal intestinal processes[8] by blocking the absorbing surface of the host's intestinal villous surface and by the production of large amounts of "*ascarase*"[32] which has an antitryptic effect, protection the parasites from being digested, but also potentially interfering with the host's ability to digest and assimilate food available in the intestines.

Venkatachalam et al[8] concluded that the loss of protein through production was negligible, but that a mean fecal nitrogen loss of 1.3 gm/day occured in children with moderate to severe ascariasis which reduced to 0.7 gm/day when the ascaris was treated. *Tripathy et al*[6,7] confirmed this and demonstrated a substantial malabsorption of fat, carbohydrate (d-xylose) and protein which improved with eradication of the worm. *Gupta et al*[33] studied 11 patients having mild round worm and concluded that at the low prevalence in community, mild round worm infections do not produce excessive gastrointestinal protein loss. Similarly, *in Soon et al* [34] studied 11 ascaris-infected, Korean children who presented light helminth burdens. Nitrogen balance studies undertaken before and after deworming on four high quality diet did not differ with respect to the absorption and retention of nitrogen.

Small bowel biopsies in infected Columbian children showed flat villi which reverted to normal after the worms were expelled. Therefore, *Tripathy et al.*[7] concluded that mucosal lesion, rather than antienzymes elaborated by Ascaris, was a possible cause of absorption defect. Jejunal abnormalities have also been demonstrated by *Maxwell et al*[31] and *Lagundoye*[30] in patients with ascariasis.

In conclusion, in the conditions when the diets are such as to meet the nutritional needs of the child, the incomplete digestion and malabsorption may not be of serious import. On the other hand, in children living on marginal diets, ascariasis must be considered as one of the contributory causes in the development of deficiency syndrome.[8]

3.8 Is the association specific? The association of Ascaris infection and malnutrition is not specific to a single cause and a single effect. Malnutrition may be due to many factors, such as improper or inadequate food intake, inadequate absorption of food, certain metabolic abnormalities, etc. In the other hand, ascariasis is known to produce vague gastrointestinal disturbance, rather than to cause malnutrition.

3.9 Is the association analogous to a previous proven causal association? Almost from the time when kwashiorkor was first recognized as a distinct nutritional syndrome, it has been associated with ascariasis.[29] Heavy infections have also been associated with stunting and avitaminosis. *Einhorn and Miller,*[12] in a clinical survey of helminthic infection among children on the Isthmus of Panama, observed malnutrition in ascaris-infected children.

In conclusion, so far, the association of Ascaris infection and malnutrition is *not clearly defined.* Because no study had been conducted with strong methodology in order for valid conclusion to be drawn about such association.

IV. A Review of Community based Studies Evaluating the Nutritional Benefits of Mass Therapy for "Ascariasis"

The effects on growth of subclinical Ascaris infection are less well understood, but of greater public health importance because of the huge number of individuals involved.

As already stated, there are many evidences indicating that ascariasis has an adverse effect on nutritional status. The public health significance of synergism between ascariasis and malnutrition *is greatest among persons who have borderline dietary status.*

Rather longitudinal analysis of the impact of an ascaricide intervention may provide the means to analyze the nutritional consequences of subclinical infections for Ascaris but even here the conclusions are uncertain (see Table 2).

In India, *Gupta et al*[22] studied the joint effects of periodic deworming and a food supplementation program on the growth of 154 undernourished poor, rural, preschool children. This group administered "tetramisole" every four months to 74 children from 2 villages while 80 control from the other 2 villages received placebo at the corresponding intervals. Both groups received nutritional supplementation. The effect of deworming on nutritional status was evaluated by comparing the initial and final weight of each child expressed as a percentage of the references weight-for-age (% R.W.A). If the final % R.W.A. exceeded the initial by 1 or more it was taken to indicate improvement; a negative difference of 1 or more indicated deterioration. At the conclusion of the 12 month intervention, nutritional status improved significantly in children subjected to periodic deworming when compared with controls. This was true for the study group as a whole and for children with stools positive for ascaris ova. This trend was significant at 8 and 12 months. Similarly, *Willett et al.*[23] reported the results of a study with 341 pre-school children in *Tanzania.* The children were randomized to tri-monthly treatment with "levamisole" or placebo for a period of one year. Anthropometric measurements were taken at each treatment interval. The rate of weight

Table 2 Comparision of Community based studied evaluating the nutritional benefits of mass therapy for ascariasis in preschool children.

Authors (years)	Location	No of treatment/control	Antihelminthic drug	Frequency of administration	Duration of observation	Reported effect on wt. gain
Cupta et al. (1975)	India	74/80	tetramisole	every months	12 mos.	positive
Willett et al. (1976)	Tanzania	166/175	levamisole	every 3 months	12 mos.	positive
Stephenson et al. (1976)	Konya	61/125	levamisole	single course	14 wks.	positive
Shah et al. (1975)	India	165/160	tetramisole	1 course	3 months	negative
Freij et al. (1975)	Ethiopia	24/60	piperazine	"	1 month	negative
Greenberg et al. (1978-1979)	Bangladeshi	93/92	piperazine	"	11 months	negative
Gupta et al. (1978)	Guatemala	39/39/40/41*	piperazine	every 2 months	12 months	negative

* control/piperazine/metroindazole/piperazine + metronidazole

gain was 8 per cent greater for those receiving "levamisole" than for placebo-treated control. The 78 children infected with Ascaris at the beginning of the study and receiving antihelminthic therapy, however, had a rate of weight gain 21 per cent greater than the subjects on placebo treatment. The rate of height gain was no different for treatment and placebo groups.

Another longitudinal study of growth in response to antihelminthic therapy was conducted in pre-school children in *Kenya* by *Stephenson et al.* [21] One-third of the children had light load of Ascaris infection and two-thirds were uninfected group (their controls) at the beginning of the trial. Anthropometric measurement were performed three times at 14 week intervals. At the second 14 week interval, all subjects received a course of "levamisole". In the 14 weeks after deworming, previously infected children showed statistically significant increases in triceps skinfold and an increased percentage expected weight gain.

Before treatment, the uninfected group (their controls) displayed a significant increase in triceps skinfold while infected group showed a decrease in triceps skinfold.

In contrast to the previous mentioned findings, *in India*[26], the effect of periodic deworming on changes in height and weight was determined in 325 Indian pre-school age children. Two villages in which the prevalence of ascariasis was 31.5 and 25 percent were divided into treatment and control villages respectively. Roughly half of the children in the treatment village then received a course of "tetramisole". The cure rate was 94 percent. After three months, no difference in anthropometry of the worm-free population versus the untreated, infected children was detected.

Another study in *urban Ethiopia*, 84 children age one to four years, no effects of deworming with piperazine could be found.[24] in this study, 44 children were positive for Ascaris ova and 40 were negative. The infected children were randomized to a treatment (n = 24) or placebo (n = 20) cohort. The uninfected group was left untreated. At a second anthropometric survey, 33 days after the administration of piperazine or placebo, all 84 children were measured. There were no differences in weight-for-age or arm circumference in the treated or untreated groups.

Similarly, in a study of 185 *Bangladeshi children* with varying intensity of Ascaris infection, *Greenberg et al.*[25] found that after 11 months treatment with a single dose of piperazine citrate, analysis of covariance revealed no significant difference for all the anthropometric variables. The cure rate and the rate of reinfection varied with the severity of infection. With more severe infections, worm eradication was more difficult and the rate of reinfection after treatment was more rapid.

More recently, *Gupta et al.*[19] concluded on a study of the effect of

treatment for multiple intestinal parasites on growth of preschool children in rural Guatemala. The study design employed "metronidazole", a drug active against Giardia and "piperazine", a drug active against Ascaris. Four groups of approximately 40 children each were randomly assigned to bimonthly treatment with placebo, piperazine alone, metronidazole alone or both drugs. After one year of intervention, piperazine decreased the prevalence of ascariasis from 60 percent to 33 percent but growth remained unaltered. Metronidazole administration decreased the prevalence of giardiasis and was accompanied by increased growth as judged by 7 anthropometric parameters.

V. Methodologic Review for the Study of Efficacy

To evaluate the efficacy of ascaricide therapeutic intervention, it is worthwhile considering to apply the 6 methodologic criteria[35] (see table 3) to the existing articles [19,21-26]

5.1 The Design Architecture

5.1.1 Random Allocation

Most of the community based studies evaluating the nutritional benefits of mass therapy for ascariasis have been limited by study design problem. There are 7 recent English language articles that tried to answer this research question. *Four* of them[19,23,24,25] were randomized trials. Among randomized trials, *three* studies[19,24,25] failed to demonstrate the efficacy of this intervention whereas only *one*[23] reported the nutritional benefits of periodic deworming in preschool children.

Both of the studies in India,[22,26] children were not randomly assigned to treatment or placebo, but rather all preschool children in two villages were treated, with children of other serving as controls. The other non-randomized trial, *Stephenson et al*[21] treated all subjects with levamisole, therefore, there was no group to serve as an untreated control. Controls were retrospectively selected and consisted of those subjects who had both negative stool examinations for the entire study period and did not expel worms after drug therapy. Comparing infected cases and uninfected controls may cause potential bias because factors influencing the prevalence of ascariasis

Table 3 The six methodologic criteria for the study of efficacy

i) Was the design architecture appropriate ?
ii) Were all relevant outcomes reported?
iii) Were the study propulation recognizably similar to your own?
iv) Were both clinical/administrative and statistical significance considered?
v) Is the manoeuvre feasible in your setting?
vi) Were all patients who entered the study accounted for in its conclusion?

may reflect unknown differences between the groups. Similarly, in the study of *Freij et al.*[24], only those subjects who had Ascaris infection were randomized, therefore, there were 2 control subgroups: uninfected and infected controls. This also may cause some bias.

5.1.2 Comparability of Study Groups and Prognostic Stratification One of the most important problems that was found in the previous studies was the way to ensure that the study groups were comparable with respect to known important variables. Because there are many important variables that may effect the outcomes, e.g. age, sex, baseline nutritional status, daily dietary intake, prevalence and severity of malnutrition, prevalence and intensity of ascariasis, prevalence of other concomittant infection, pattern of illness, socioeconomic status, history of previous immunization and breast feeding, numbers of children in the family and birth rank of the child, mother's education and seasonal variation. Most studies cannot compare all of these factors for their study groups. Some of these articles used *prognostic stratification* in term of age, degree of malnutrition[24,25] and intensity of Ascaris infection[25] prior to randomization.

5.2 Outcomes It is agreed that Ascaris infection causes widespread and very important morbidity. However, objective measure of the morbidity is very difficult and there is relatively little factual information concerning it.[29]

All studies assessed nutritional status in term of "*anthropometric indicators*" that appears relevant and objective outcomes. By general concencus of those working in this field, *nutritional anthropometry* has a most significant role in the direct assessment of nutritional status of communities, especially in cross-sectional survey in young children in less developed countries, where the problem of malnutrition is most severe and extensive. because anthropometry can assess the existing nutritional status by measuring total body mass and body composition and it can follow for the community of trends of ecological factors, including nutrition, through periodic measurement of anthropometric characteristics of growth and development.[1]

However, *determination of age* in age-dependent anthropometry, that were used in all studies, is rather difficult to ensure reliability, especially in rural area of developing countries where register system is not well organized.

In the Kenya study[21], they based their conclusion primarily on skinfold measurements, the significance of which is doubtful.

All randomized trials[23,24,25] except one, outcomes were *assessed blindly*. However, no information on inter- and intra-observer variation were considered.[19,23,24]

5.3 The Study Patients Although most studies.[19,21,22,23,25,26] were conducted in rural community where malnutrition and Ascaris infection are both common, the study patients are difficult to recognize the similarity between them and other rural community due to insufficient details of some important information, such as eligibility criteria, sociodemographic data, intensity of Ascaris infection[23], and degree of malnutrition[19,22,23,24,26] in those communities. Without such details, these results cannot be generalized to one's own setting.

5.4 Results There were 3 existing articles that reported significant improvement in growth after treatment with a single course of ascaricide[21,22] and periodic deworming[23]. In contrast to these findings, four recent studies[19,24,25,26] reported no significant benefits from a single therapeutic intervention[24,25,26] and periodic intervention[19] of ascariasis. If we consider only 4 randomized trials,[19,23,24,25] the best design to demonstrate efficacy, we will have 3 negative trials and only one positive results. However *single therapeutic intervention are limited* by the fact that in an Ascaris endemic community, there may be frequent movement from non-infected to infected status and vice versa[17]. *Greenberg et al*[25] reported the rate of reinfection after treatment varied with the severity of infection. Therefore, *single mass treatment in an Ascaris endemic area may not justify* for the future implementation. Thus again, considering the studies that performed periodic deworming in their intervention, we have only one positive and one negative randomized trials[19,23] (see figure 1). Unfortunately, in the negative randomized trial of *Gupta et al*[19] the number of children was not big enough to show a clinically significant difference if it should occur.

5.5 The Manoeuvre

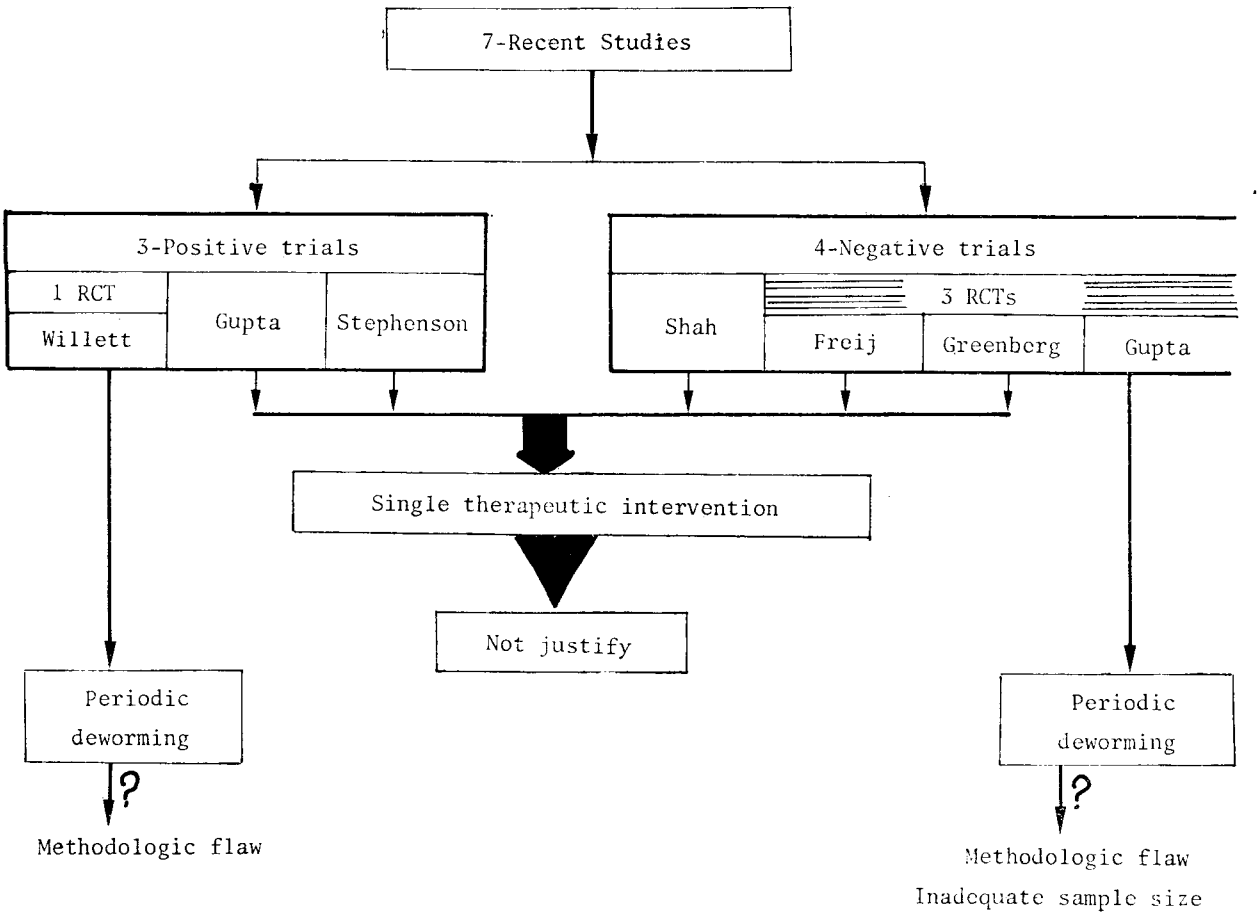
5.5.1 Replicable description of manoeuvre Although most studies described the manoeuvre in sufficient details, no studies addressed the side-effects and toxicity of the given medication. Levamisole may have potential immunostimulatory effects and the possible related effect on growths[25]. Likewise, neurological side effect have been reported with piperazine.

5.5.2 There are not enough data to assess the question whether how long with what clinical criteria for deciding that therapy should be given, increased, tapered or terminated?

5.5.3 Co-intervention This bias is likely to occur in the studies that were not double blind.[19,21,22,26]

5.5.4 Contamination All studies did not describe how contamination was resolved or even controlled for. The patients in the control group may accidentally receive antiascaris

Figure 1
Summary of the community based studies Evaluating the nutritional benefits of mass therapy for ascariasis in preschool children



treatment from the other source. Therefore, the reported spontaneous loss of ascariasis in control group in most papers probably resulted from natural attrition of the adult worm (life span of about 1 year) and unregulated antihelminthic treatment from other source.

5.5.5 Patient Compliance Some studies, drug (or placebo) was given directly by their health personnels to ensure patients compliance.[19,23] Nevertheless, compliance was not adequately dealt with especially for those patients who lost to follow-up during periodic examinations or those patients whose stools were not examined.

5.5.6 Follow-up In some studies,[21,24] the follow-up period was insufficient to detect a significant difference over a short period of time.

5.6 Accounting for all patients All positive trials,[21,22,23] the patients who entered the study were not accounted for at its conclusion.

Table IV

Methodologic Review for the Study of Efficacy

Methodologic issue \ Investigators	Gupta (22)	Stephen-son (21)	Willett (23)	Gupta (19)	Freij (24)	Green-berg (25)	Shah (26)
			RCTs				
			Periodic deworming		Single course		
Design architecture:							
Random allocation	x	x	✓	✓	✓	✓	x
Comparability of study grs.	?	?	?	?	?	?	?
Prognostic stratification	x	x	x	x	✓	✓	x
Outcomes:							
Relevant	✓	✓	✓	✓	✓	✓	✓
Blind assessment	x	x	✓	x	✓	✓	x
A searches for toxicity of med.	x	x	x	x	x	x	x
The study patients:							
Similarity to your own	?	?	?	?	?	?	?
Results:							
Clinical/Statistical sig.	✓	✓	✓	x	x	x	x
Adequate sample size				x	x	?	x
Manoeuvre:							
Replicable	?	?	?	?	?	?	?
Possible co-intervention	✓	✓	x	✓	x	x	✓
Possible contamination	✓	✓	✓	✓	✓	✓	✓
Ensure pts. compliance	x	x	x	x	x	x	x
Accounting for all pts.	x	x	x	✓	✓	✓	x

✓ = yes
x = no
? = can't tell

VI. Conclusion and Implication

Although control programs for ascariasis should ultimately aim at environmental sanitation and personal hygiene, for many reasons, *Ascaris control is not easy to achieve in our country.* Past attempts to control helminthic infections in poor rural communities using improved sanitation and health education have *largely failed.* Therefore, if we can demonstrate the nutritional benefit of the periodic deworming intervention, this intervention seems worth introducing program in *selected areas where malnutrition as well as ascariasis are both common in preschool children.*

Unfortunately, community based studies evaluating the nutritional benefits of mass therapy for ascariasis in preschool children are still unclear whether deworming programs would always have a beneficial nutritional effect. While some studies have shown significant improvement after single periodic deworming, others have revealed no significant changes at all. Considering single therapeutic intervention is not justified, we only have 2 randomized trials, one positive and one negative, that performed periodic deworming as part of their intervention. Both apparent ambiguous studies have not been conducted with an adequate methologic rigor to reach a valid conclusion. Furthermore, the negative trial had no adequate power to back up the author's conclusion. Therefore, further research in this area is really needed.[36,37]

However, these studies can serve as guides to improve the experimental design in the future studies that might provide more significant answer.

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