School-based supplementation studies addressing anemia among adolescents in Indonesia
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Citation for published version (APA):

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CHAPTER 8

Overview and Conclusions
The studies described in this thesis were implemented as part of the OMNI (Opportunities for Micronutrient Interventions) project (1), which aimed to assist countries worldwide in meeting the millennium goals of virtually eliminating, by the year 2000, both vitamin A and iodine deficiency and their related consequences and reducing by one-third the 1990 levels of iron deficiency anemia in women (2). More broadly, the reduction of malnutrition is now specified as a key component of reducing global poverty. This is reflected in the United Nations Millennium Development Goals, which aim at sustaining development and eliminating poverty (3,4). Malnutrition and poverty are interlinked (5); not only does poverty cause malnutrition, but malnourished individuals are economically more vulnerable due to their suboptimal physical and mental development. Therefore, poverty reduction will lead to improved child nutrition and to enhanced human capital, which in turn will increase productivity and thus contribute to further reduction of poverty (6). Poverty plays a central role in the vicious cycle of malnutrition and associated morbidity throughout the lifecycle as malnourished mothers give birth to malnourished children who grow up to be malnourished adults. One way to break this intergenerational cycle of malnutrition is to optimize the nutritional status of adolescent girls, prior to conception.

Within the OMNI framework, the studies described in this thesis addressed one of the available strategies (supplementation), with the novel target group of adolescents. The hypotheses on which the design of the studies was based, were that 1) anemia and subclinical vitamin A deficiency are prevalent among adolescents, that 2) supplementation with iron and vitamin A are effective to treat these conditions, and that 3) schools are a good channel to reach adolescents.

The first hypothesis was proven to be true, not only by the current studies, (chapters 3, 4, 5, 6) but also by others (see literature review in chapter 7). While there is no doubt as to the efficacy of iron and vitamin A supplementation (7; chapter 7), this did not automatically lead to good effectiveness (chapters 4, 5, 6). Although it is true that a large proportion of Indonesian adolescents can be targeted through schools (8), the implementation of a supplementation program using this channel needs to overcome many challenges.

This chapter discusses the results of the studies described in this thesis from a science, policy and programs perspective. At the end of the chapter, the main conclusions are presented together with implications for policy development and recommendations for future research.
SCIENCE: THE NEED FOR, AND EFFECTIVENESS OF, SUPPLEMENTATION

1. Anemia prevalence among adolescent boys and girls

In the current studies sex differences were found in prevalence of anemia among adolescent boys and girls, being higher in the latter. This is consistent with data from the International Nutritional Anemia Consultative Group (9).

Not much is known about the prevalence of anemia among adolescent boys. However, the relationships between age, hemoglobin and pubertal status as found in this study population (chapter 3) are similar to those reported earlier (10). Among pre-pubertal boys, anemia prevalence was significantly higher than among pubertal boys, even when corrected for age (chapter 3). This difference, and the lower anemia prevalence among pubertal boys compared to girls, can be explained by the physiological increase in hemoglobin concentration caused by sexual maturation of boys (11), as well as by decreasing requirements after completion of the growth spurt. In girls, any expected age-related increase in hemoglobin concentration is halted by the onset of menstruation and the ensuing regular blood loss. Also, the growth spurt occurs much earlier among girls (chapter 2). Therefore, no difference in hemoglobin concentration was found between among pre-pubertal and pubertal girls in these studies.

The recommended nutritional intakes for adolescents do not distinguish between different maturity phases. Because of the dearth of data on adolescents, estimated average requirements are extrapolated from adult data. Growth and menstrual losses are taken into account and apparently the recommendations are made based on an estimation of the proportion of pubertal subjects per age group (12). The observations in East Java show that this is appropriate for girls (as hemoglobin concentrations did not differ with maturity). However, the higher anemia prevalence among pre-pubertal boys suggests that they in fact have higher nutritional needs compared to pubertal boys at the same age.

Supplementation interventions do not take these differences into account and consider adolescents as a homogeneous group. Obviously, to do this would be difficult for a well-controlled trial and almost impossible for a supplementation program. However, the absence or presence of impact of supplementation should be viewed against this background of varying requirements in the target population.

2. The need for supplementation

The literature review clearly illustrates the paucity of surveys and studies among adolescents (chapter 7). However, all available data are consistent in showing that anemia
among adolescents is a public health problem. Because of the detrimental effects of anemia, both on the individual development and on that of future generations, interventions are urgently called for. Supplementation is the most suitable intervention as it is cost-effective and effects can be expected to take place within a few months.

3. **Supplementation is efficacious**

   At the time the current studies were designed, no intervention studies with iron in adolescents had been published. Even now, only a very small number of intervention studies have been reported on (chapter 7). Of these, only two included vitamin A supplementation. Ahmed et al (13) compared weekly supplementation with 120 mg iron and 350 µg folate with 8000 IU vitamin A and the combination in a strictly randomized trial among anemic adolescent factory workers. Angeles-Agdeppa et al (14) compared daily and weekly supplementation with the combination of vitamin A and two different doses of iron among adolescent girls attending Senior High School. They both found weekly vitamin A with iron/folic acid efficacious in increasing Hb, serum ferritin and serum retinol. This finding is consistent with what is known about the interaction of iron and vitamin A (7). The lower dose was preferable because of its lower level of side effects (14).

   Of 16 studies reviewed, only eight provided sufficient information and were sufficiently well-designed to draw conclusions from their findings, including the three intervention studies described in this thesis (chapters 4, 5, 6). The conclusion of the review is that the optimal regime is a combination of at least iron, folate and vitamin A given weekly using tablets containing 60 mg iron. The studies described in this thesis complied with this recommendation.

4. **Effectiveness of supplementation**

   In the first study (chapter 4: weekly supplementation for 14 weeks with 60 mg iron and 250 µg folate, 10,000 IU vitamin A or both) none of the regimens resulted in an improvement of hemoglobin concentration. After adjustments to the study design (chapter 5: extension of duration of weekly supplementation to 22 weeks, increase of vitamin A dose to 20,000 IU, and the introduction of a placebo group and the use of sugar coated tablets), both sexes in the urban area benefited from supplementation, but not in the rural area. The combination of vitamin A and iron proved to be most effective. In the third study (chapter 6: supplementation with iron/folate combined with nutrition education) there was an increase in mean hemoglobin concentrations among adolescent boys but not among girls.

   In the first study, a non-significant increase in serum retinol concentration was found in boys but not in girls (chapter 4). In the second study, no impact on serum retinol concentration was found in either sex (chapter 5). While compliance will have played a role,
this can not entirely explain this lack of effect. It is hypothesized that the timing of blood sampling was too late in relation with the end of the supplementation \((15)\) and supplemental vitamin A was already used or stored and not found in the circulation anymore. Another possibility is that the subsample was not representative of the total study population. In either case, the protocol or timing of blood sampling used was not adequate to measure impact of the intervention on serum retinol.

5. Difference with the literature

The differences found between the studies described in this thesis and other published studies are mainly due to the fact that the other studies were efficacy trials. Besides strictly supervising of compliance, most of these studies only reported on those subjects who complied well, as determined by compliance checks (mostly left-over pill counts). In contrast, the objective of the current studies was to determine the effectiveness of supplementation (assuming its efficacy in the target population, which was later shown by others) in a program setting. It was found that compliance had a major impact on the effect of the interventions on hemoglobin and serum retinol concentrations.

Thus, the results of the studies described in this thesis show that applying an efficacious approach in a routine program setting does not necessarily yield the desired results. In a program one should take into account some additional factors besides efficacy, and randomized controlled trials should not be considered the only method of evaluation of effectiveness.

POLICY ISSUES

1. Adolescents as target group?

At the time the current studies were designed, focus of micronutrient interventions was on pregnant women and underfives. The awareness of the suboptimal success of this approach was dawning and adolescent girls came into view as a means to improve pre-conception nutritional status. The results described in this thesis underscore the need to acknowledge adolescents as a target group in their own right, irrespective of reproduction. In the comprehensive life cycle approach a relevant targeting would be geographically (urban slum area or poor rural areas) or by risk families (including all members). Either way, the adolescent age group should be included in both assessment surveys of the extent of (micronutrient) malnutrition and interventions aimed at reducing the prevalence of those deficiencies.
The studies in this thesis were only concerned with school-going adolescents. Although in certain settings, such as in Indonesia, the vast majority of younger adolescents still attend school, those who have dropped out are likely to be more seriously affected by poverty and malnutrition. However, it was outside the scope of the current studies to address this important group as well.

2. Inter-departmental approach

While the health system is an appropriate channel to approach pregnant women and underfives, this is not the case for adolescents, who generally feel healthy and are therefore less likely to use health facilities. Therefore, employing alternative channels (such as schools, work sites or social groups) is essential. As the health sector is responsible for micronutrient supplementation, collaboration and coordination between relevant sectors are essential (see next section, Program issues).

3. Supplementation is not a short-term approach

The studies in this thesis were concerned exclusively with supplementation. The reason was that it is important to address the problem of anemia among adolescents in a way that will be relatively easy to implement and will yield good results within a reasonably short period of time. Dietary change, although the most ideal solution, is highly dependent on availability and affordability of high quality foods and will therefore remain a distant dream for a large proportion of the world population for some time to come. Fortification of certain foods with micronutrients is promising. However, it will take some time before all problems regarding technical issues, taste and, in particular, price are solved. Those most in need will be least likely to benefit from food fortification, breeding and genetic manipulation efforts, at least in the near future. Thus, supplementation will be the intervention of choice as long as diets remain of poor quality. Ultimately, only by reaching the Millenium Development Goals will it be conceivable for blanket/large-scale supplementation efforts to start phasing out. However, it should be noted that in many developed countries, such as the Netherlands, the use of supplementation for children with vitamins A and D in ‘months with an R’ continues to this day.

Most efficacy studies to date have restricted themselves to anemic subjects. However, from a public health and cost point of view, it may be worthwhile to target the whole population to have an impact among a subgroup, rather than identify subjects at risk and then specifically target those.

4. Need to discuss and communicate results of program evaluations

In order to decrease the time that elapses between research, program evaluation and
policy formulation, more effective communication strategies should be put in place. Findings should be discussed and communicated with all key partners in the program, including also scientists and international and donor agencies. Scientific platforms should be created to discuss various aspects of the program evaluation. Scientific meetings, special editions of scientific journals or textbooks with experiences from the field are examples of possible platforms (16).

PROGRAM : REQUIREMENTS FOR SUCCESS

In this section, first, the key partners in a program will be identified and aspects of program design and implementation related to them will be discussed. Then, logistic challenges for school-based supplementation programs and possible solutions are presented. Finally, monitoring and evaluation needs are discussed.

1. Key partners in program implementation

Many players are involved in school-based interventions, and it is essential that all parties are fully committed to the undertaking. Students, parents, teachers, school administration, and all ministries involved (Health, Education, Religious Affairs, Financial Affairs and possibly others depending on the local situation) at both central and local levels should be active participants. If possible, representatives of all parties should be involved in the program development and implementation.

Programs should be focused on the health needs and perceptions of the target population rather than on the ideas of scientists or policy makers. Therefore, the problem to be addressed by the program should first be clearly defined in a way that reflects the needs of the target population. For example, a social marketing campaign to increase consumption of vitamin A-rich foods in Central Java, Indonesia promoted eggs and dark green vegetables for healthy and smart underives (17). In the case of adolescents, the problem could be defined in understandable terms of suboptimal academic achievements, poor school attendance, or poor physical productivity. These problems are all related to poor nutrition and will lead to increased poverty in the future. In addition, they can easily be measured objectively, providing clear outcomes for all those involved.

By defining the problem together with all key partners, and by thus ensuring the political will and commitment to address it, it will be easier to design and implement the most appropriate intervention(s). As mentioned above, school-based supplementation intervention requires an inter-departmental approach, which in certain settings is still a novelty. It will
depend on local situations in individual countries whether this can be reached. Obviously, awareness of the seriousness of the defined problem in combination with the cost-effectiveness of the proposed intervention, are important for the allocation of the required financial means to implement the program.

The schools, more precisely the teachers, will be the providers in a school-based supplementation program. In order for the program to be successful, it should be part of the teachers’ job description and all teachers in the schools should be aware of the problem (the prevalence of anemia and the consequences for health and both physical and academic performance of adolescents) and the benefits of the proposed intervention, as well as have the necessary skills for nutrition guidance. The program should ideally be integrated in normal school routine in order to prevent a sense of being overburdened. However, the supplementation (and nutrition education) activities will still be an additional task for the (often underpaid) teaching staff. Therefore, new ways to raise awareness among the teachers are called for. Not only will they need extra training to increase their understanding of the consequences of anemia, but they should also feel a personal benefit. Providing supplements to the teachers and their family members as well (as was done occasionally in our studies) proved to be a good way to enthuse them, as they could feel themselves the benefits of the tablets. In the competitive educational system in Indonesia, final grades of their students are important to schools. As the school’s status increases, its financial situation improves, which can be used as an incentive to the teachers. Providing educational materials about the problem and solutions for anemia and its consequences that are of good quality and have an appealing form and lay-out to use in the lessons can also increase the pleasure the teachers take in their work. Obviously, these suggestions should be worked-out in the particular local situation.

As the ones ultimately responsible for their children, parents should be made aware of the problem of anemia and the benefits of the supplements. In this way, mothers will not take the supplements meant for their adolescent daughters, but rather they can support the students by encouraging them to take the supplements, in particular during holidays, and even be directly involved as program volunteers.

Finally, the students are the target population for the supplementation. So far, in most studies and many programs, the client perspective has been neglected or not given the importance it deserves. The studies presented in this thesis illustrate that the effectiveness of a supplementation program is directly related to the compliance of the target population.

2. Practical considerations

If supplements are to be taken under supervision, drinking water should be available at all schools. In the schools involved in the current studies, and most schools in Indonesia, this was not the case. There are several ways to provide drinking water at the schools, some of
which were tried in the studies described in this thesis. None were ideal, and some were
effective in some schools while others were effective in other schools. One way is to have
water dispensers (using gallons) available at the schools and each student has his/her own
cup/glass, which can be filled with enough water to take the supplement. However, it is
difficult to ensure that sufficient water is always available at the time the supplements should
be taken, and to train all students to always bring their cup. Alternatively, sealed cartons of
drinking water packed in 200 ml glasses can be distributed to the schools. While ensuring the
availability of sufficient water this causes a considerable waste problem. In addition, both
these solutions are costly. Where it is possible to provide clean water, or other drinks, as a
cooperative effort between different programs (e.g., face washing component of SAFE
approach for Trachoma control, school feeding initiatives), this could help to solve this
problem.

The level of involvement of the teachers was highly variable both between and within
schools. In Indonesia, there is a tendency of thinking in departments and many teachers felt
no ownership of this health activity. Possibly, with more intensive communication and
specific training for the teachers this can be overcome. Although some teachers understood
from the start the positive implications for the health and academic achievement of their
pupils, for others even financial incentives only partially eased their feeling of being
overburdened by yet another task. The presence of teachers has been shown to enhance
compliance (18-20). However, in the studies described in this thesis, teachers were hard to
involve and did not feel ownership of the program. Both would be addressed, if the
intervention was included in their job description, which is a macro-level policy.

Planning a school-based intervention, whether as a study or as a program, requires
flexibility. The schools have their own schedules to adhere to and in particular data collection
activities are highly disturbing to the school routine. This sometimes makes coincidence with
holidays or the Muslim fasting month inevitable, leading to the choice between unsupervised
or discontinued supplementation. However, in the context of a long-term, continuing program
this is less of a restraint than in a randomized controlled trial.

3. Compliance: an important determining factor for effectiveness

Effectiveness of supplementation is the product of efficacy of the supplement,
efficiency of the intervention and compliance. Supplement efficacy has been shown by others
(14,21) and there was no problem with availability of the supplement. Therefore,
effectiveness was highly dependent on compliance in taking the supplements.

Compliance in the current studies was found to be inversely related to side effects. In
the first study (chapter 4), 41.4% of girls and 24.3% of boys complained of side effects,
compared to only 8.8% and 4.4%, respectively, in the second study with sugar-coated tablets
Self-reported compliance for supplements taken without supervision was 31.3% among girls and 27.2% among boys in the first study (chapter 4). In the second study, this was 66.9% and 65.2%, respectively (chapter 5). However, this improvement was not seen among those who had also participated in the first study, probably due to disbelief that the sugar coated tablets would not cause similar side effects to the previously used, non-sugar coated tablets.

A sex difference was found not only in the level of compliance, but also in the students’ attitude. In all three studies (chapters 4, 5, 6), boys more overtly refused the tablets, while girls made the impression of complying, while in fact they did not swallow the tablets, but threw them away or gave them to their mothers.

There also appeared to be an urban/rural difference in compliance reporting, for which no explanation was found. In the second study (chapter 5), 56.9% of the subsample of rural girls reported having taken at least 75% of the unsupervised tablets, compared to 69.7% of urban girls (p<0.10). Among boys, percentages were 53.8 and 70.6, respectively (p<0.05).

Peer pressure was strong and oriented towards non-compliance, while teachers’ involvement was suboptimal. Supervision appeared to have a stimulating effect on compliance (chapters 4, 5, 6). This is in line with the results of Angeles-Agdeppa et al (14), although Muro et al (22) argued that the students’ increased sense of confidence and responsibility in an unsupervised but ‘coached’ supplementation study had a highly positive effect on compliance.

4. Advocacy and social marketing as key elements of program design

The above illustrates that advocacy and social marketing are essential elements in awareness and demand raising, program design and implementation. In order to achieve full commitment, advocacy based on scientifically obtained facts is essential. Special social marketing and education for teachers need to be designed and implemented, starting before the supplementation is implemented and repeated at regular intervals. The same holds true for the students and their parents, as illustrated by an example from Tanzania (22). However, the results of the third study (chapter 6) also indicate the need for gender-specific messages to improve compliance among adolescents.

Behavioral change requires time and appropriate messages in an appropriate form. When implementing school-based interventions, nutrition education through schools is an obvious choice. However, in particular if other channels than schools are utilized, it is important that innovative channels of delivering social marketing messages are explored. As the target population consists of adolescents, one could consider popular songs or comics. Advertising in mass media (including tabloids, radio, television) is another option, as are direct communications through (religious) groups for youths, women, men. A different
approach would be to address the issue of adolescent health and nutrition in a television soap. These are highly popular in Indonesia, in particular among girls and women.

5. **Monitoring and evaluation of programs**

The only way to assess whether programs are effective is to implement rigorous monitoring and evaluation, using well-defined outcome indicators, in addition to process indicators. By continuously assessing the effect as well as factors that are contributing or obstructing the successful implementation of a program, informed decisions can be made to modify, continue and expand programs.

However, there is still a need to further develop adequate and feasible approaches for program evaluation, and to quicken the process from research to policy and programs (16). In general, there are three ways to evaluate the impact of a program: adequacy, plausibility and probability assessment (23). Where probability assessments (concerned with occurrence of expected changes and their statistical significance) are widely used in randomized controlled trials, the plausibility approach, which assesses whether the program seemed to have an effect above and beyond external influences, is not.

The advantages of the plausibility approach is that it can be used when randomization to treatment is not possible, for ethical reasons (as in some of the studies reviewed in chapter 7), because the treatment can not be blinded or the program has already started. Plausibility can only be demonstrated if all other likely explanations for the observed improvements can be formally discarded. The plausibility that the intervention was the cause of the impact found can for example be shown by dose-response relationships within treatment groups, changes over time, and/or concurrent changes in multiple indicators or processes.

**CONCLUSIONS AND RECOMMENDATIONS**

1. **Prevalence of anemia**

   **Conclusions**
   
   i. Only limited information is available on the prevalence of anemia and other micronutrient deficiencies among adolescents in developing countries, and this mainly covers menstruating girls. Nevertheless, existing information consistently reports high prevalence of anemia among adolescents worldwide (chapter 7);
   
   ii. Based on even fewer reports, the same holds true for vitamin A deficiency, and most probably also for other micronutrients (chapter 7);
   
   iii. These deficiencies are related to poor socio-economic status and originate from insufficient dietary intake (chapters 3, 5, 7);
iv. Both the prevalence of anemia and vitamin A deficiency, and the relationship with socio-economic status were confirmed in the study population, while the relationship between anemia and puberty was demonstrated in boys and girls (chapters 3, 4, 5, 6);

Recommendations
i. Further research is needed to determine prevalences of micronutrient deficiencies, in particular iron, vitamin A and zinc among adolescents, both boys and girls. This can be done by conducting surveys of adolescents, but also by including adolescents, as part of the life cycle approach, in the assessment of micronutrient deficiencies of Demographic Health Surveys;

ii. Data with regard to adolescents should be reported separately per sex, age and maturity phase (recommended indicators for field studies are discussed in chapter 2), and sampling frames should take into account differences in socio-economic status (chapter 3);

2. Supplementation

Conclusions
i. The most appropriate approach to control anemia among adolescents in the near future is consumption of micronutrient supplements;

ii. From the very few well-designed efficacy studies of supplementation among adolescents, it appears that weekly supplementation for at least 12 weeks is at least as efficacious and effective as daily supplementation in increasing hemoglobin concentrations and iron stores, while it is associated with fewer side effects and lower costs (chapter 7);

iii. Weekly supplementation with 60 mg iron, 250 μg folate and 20,000 IU vitamin A for 22 weeks was effective to increase hemoglobin in urban boys and girls, and serum retinol concentration in adolescent boys, in particular those with low serum retinol concentrations (chapter 5);

Recommendations
i. School health programs, including supplementation for anemia control are called for;

ii. Supplementation interventions should be universal and not focused on certain groups of adolescents;

iii. The need and feasibility of multiple micronutrient supplementation should be assessed;

iv. Supplementation should be given on an ongoing basis, as a long-term intervention.
3. Programmatic aspects

Conclusions
i. There was a sex difference in response to iron and vitamin A supplementation, probably due to differences in compliance, which should be investigated further (chapters 5, 6);
ii. Gastro-intestinal side effects appear to play an important role in decreasing compliance. The use of sugar coated iron tablets greatly improved compliance by reducing side effects (chapters 4, 5);
iii. Previous experience with side effects of supplements can negatively influence compliance for a long time, even if the tablets are improved (chapters 5, 6);
iv. More intensive supervision and continuing nutrition education seems to increase compliance among adolescents, especially boys (chapters 4, 5, 6);

Recommendations
i. Studies of iron supplementation among adolescents should focus on effectiveness rather than merely on efficacy;
ii. The client perspective (in this case of students, teachers and the community) should be included in program design, implementation, monitoring and evaluation;
iii. All supplementation programs should be adequately monitored and evaluated to assess effectiveness and to identify the best communication strategies to achieve optimal compliance;
iv. Inter-departmental coordination and cooperation between (at least) the Ministries of Health and Education should be ensured for school-based health programs;

4. Social marketing

Conclusions
i. Awareness-raising in the general population by social marketing is necessary to reinforce an institution-based approach such as school-based supplementation;
ii. Social marketing can cause a behavioral change among adolescents regarding their own responsibility to achieve good health and nutritional status and the role that interventions can play;

Recommendations
i. Advocacy and social marketing should focus on raising awareness of the importance of adolescent health and behavioral change;
ii. Messages should be focused on the target group and this might mean that gender-specific messages are needed. Therefore, the optimal communication strategies in mixed groups of adolescent girls and boys need to be determined in relation to the cultural context (chapter 6).
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