

***Pill Taking Behavior:
Implications for Micronutrient
Supplementation for Safe
Motherhood***

A Literature Review

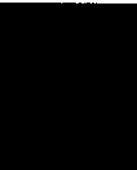


**Pill Taking Behavior:
Implications for Micronutrient
Supplementation for Safe Motherhood**

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Introduction

Over the past decade, increasing attention has been placed on the potential for micronutrient supplementation to reduce maternal mortality and morbidity. Vitamin A supplementation has been demonstrated to reduce maternal mortality (West). Iron supplementation is efficacious in improving hematologic indices and reducing maternal anemia (Sloan, Yip). Calcium appears to be effective in reducing pregnancy-induced hypertension (Carroli, Guyatt). Zinc supplementation appears promising for the reduction of maternal infection (Shrimpton, Yip). Iodine supplementation reduces goiter and congenital cretinism (WHO). Prenatal folate supplementation reduces neonatal neural tube defects.

The effectiveness of micronutrient supplementation greatly depends upon the supplements' supply and delivery systems and on pill taking behavior. Food fortification has been a successful long-term delivery system for improving nutritional status in the United States and Europe, but may be problematic to implement on a large scale in non-industrialized countries (Sethuraman, Arroyave). Dietary modification is another long-term approach to improving nutritional status, but is dependent on many factors and has had qualified and variable levels of success (Willett).

Periodic distribution of micronutrient supplements remains an important short to medium term strategy due to the delivery systems' affordability and implementation feasibility. WHO and OMNI have suggested integration of micronutrient supplementation and other reproductive health services (WHO). Multiple daily or weekly supplements (to provide the amount of supplements necessary to cover monthly, quarterly or semiannual needs) can be provided through periodic delivery. Special precautions need to be taken, however. Unlike vitamin A supplementation for children or postpartum women, periodic delivery of single megadose vitamin A, iron, calcium and zinc is contraindicated as these nutrients may be toxic if consumed in excess by children or adults, particularly pregnant women (Rosso, Shils). Excess intake is generally limited to the period in which supplementation is initiated (Ekstrom), but is a common occurrence (Cramer, Ekstrom). These precautions include adequate evaluation of the:

1. Acceptability, safety, effectiveness and costs of the supplement regimen and distribution system, and
2. Biologic interactions, compliance, effectiveness and costs of multi-micronutrient supplements (combined vitamin A and iron, iron and calcium, etc.).

Additionally, the relative effectiveness and costs of alternative approaches, such as prevention and treatment of hookworm disease and malaria, should be compared to supplementation to reduce long-term micronutrient deficiency.

This report reviews current knowledge of pill-taking behavior, what is known about compliance with daily compared with weekly pill-taking, duration of prescribed supplementation and adherence to the regimen, overcompliance and safety, side effects, effectiveness. The report discusses the pros and cons of targeting vulnerable periods and population groups, and the theoretical cost differentials of different regimens. General considerations for recommending

service delivery protocols and regimens that are the most effective, feasible, acceptable, affordable are discussed. Operations research that needs to be conducted prior to recommending and implementing micronutrient supplementation programs to improve safe motherhood is described.

This paper reviews key references that focus on pill taking behavior and its implications for improving safe motherhood through nutritional supplementation, with particular emphasis on developing countries and where possible, pregnant and lactating women. The paper also differentiates between theories and evidence about why people do and do not take pills as prescribed.

Pill Taking Behavior

Pill taking behavior has been studied by sociologists, anthropologists, clinicians, demographers, psychologists, and epidemiologists using a variety of methodologies (observation, self-report, physician perception, pill counts, biologic markers, electronic monitoring systems) for a multitude of conditions (anemia, heart disease, epilepsy, malaria and others). Indirect methods to assess compliance (self-report, physician perception, pill counts) have been found to generally overestimate compliance (Cramer, Sbarbaro, Wright). While pill counts may be the more objective of these methods, the number of residual pills does not provide information on the actual use of the pills, which could be given to other individuals, animals, or simply discarded. Spot checks have been used to improve these measures, but may be limited to pill counts unless anthropologic measures permitting consistent observation are used. Observation and supervision have been used for nutritional studies (Charoenlarp, Sommer, Willett), but these are generally limited to studies of efficacy (that measure maximum effectiveness under the best conditions possible) or studies to measure the reliability of dietary intake or the validity of self-reported or food frequency methods to determine dietary intake. More objective methods are amnestic measures (biologic markers) and electronic monitoring. Biologic markers have been used (Cramer, Porter, Rush) but may be problematic if the regimen's half-life is limited and the supplement has not been consumed on the previous day. This is a particular problem for measuring compliance with periodic regimens. More recently, medication electronic measuring systems (MEMS, i.e., medicine bottles specially prepared with electronic counters to record the exact day and time the bottle is opened and medicine used) have been used (Cook, Cramer, Ekstrom, Potter) and are thought to be the most reliable method to estimate pill taking behavior. The electronic monitoring method is not without problem, however, as the bottle alone may influence compliance. In addition, data capture using MEMS is troublesome. Potter found 18% of bottles were not returned and valid data could not be retrieved from 20% of the returned bottles. Loss of data might be attributable to misuse of bottles (and poor or inaccurate compliance).

Pill taking behavior has received much attention in the literature, although it has less often been well measured and quantified. Compliance (or adherence) to prescribed regimens has been the measure by which pill taking behavior has been most commonly described and evaluated. Compliance takes many forms, including initial acceptance or rejection of the regimen, taking

the correct number of prescribed pills, in the correct manner, and with the correct continuation of the regimen over time (Cramer, Potter).

Multiple factors influence pill taking behavior. Particular attention in the literature include:

- Frequency,
- Duration of regimen,
- Dose,
- Side effects/adverse reactions,
- Perceived importance/effectiveness of prescribed medication,
- Information/comprehension of correct regimen,
- Availability,
- Appearance/packaging,
- Cost, and
- Forgetfulness.

Compliance: Facts and Theories

Table 1 summarizes data identified through a medline search of literature from 1950 to 1997 on compliance with vitamins, minerals, anti-malarials and oral contraceptives and from references identified in that literature.¹ Data from all identified studies conducted in developing countries quantifying pill taking compliance of pregnant and lactating women are included in this report, as well as data from other identified studies where data for pregnant and lactating women or from developing countries were scant. These studies include information from evaluations of preventive medications including iron supplementation, multivitamins and prenatal vitamins, vitamin A, anti-malarials and oral contraceptives. The text also includes some comparative information regarding adherence with medications used for treatment and prevention of other conditions including high blood pressure, epilepsy and others.

Frequency

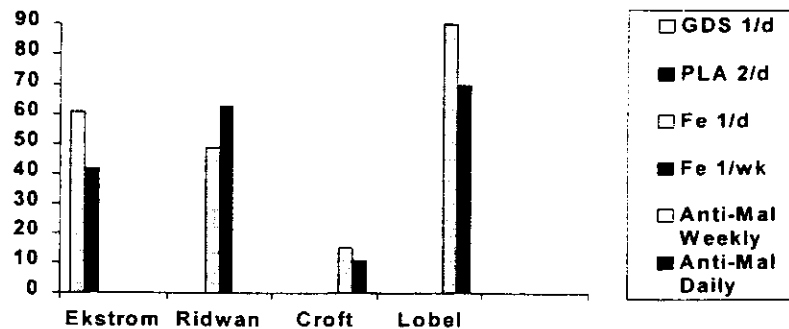
The frequency, simplicity and regularity of regimens affects compliance (Harper, Cramer, Porter). Fewer daily doses have been associated with better compliance in studies that have measured and presented data comparing groups receiving regimens of different frequencies or complexities. Ekstrom, Ridwan and Simmons present relevant data for iron supplementation in pregnant women attending antenatal clinics in rural Tanzania, Indonesia and urban Jamaica, respectively. Ekstrom et al. found compliance, measured by an electronic measuring system with a single daily dose of a gastric delivery system (GDS) for iron supplementation was 61% compared with 42% in controls with a twice daily dose, one in the morning and one in the afternoon, of supplemental iron. The difference in compliance cannot be entirely attributable to the difference in side effects, as compliance continued to be greater, 44% vs. 30%, in the daily compared with twice daily regimen in the subgroup of women experiencing side effects. Some of the difference in compliance may have been associated with other factors, such as difference

¹ References that could be obtained within 14 days of the search.

in appearance of the GDS and routine supplements (discussed below). Ridwan found reported compliance with daily iron-folate supplementation to be 49% compared with 63% in those taking a weekly supplement including one morning and one evening dose, once per week. Simmons found the drop-out rate was highest, 30%, in those assigned to the twice daily, one morning, one evening, GDS compared to once daily regimen of the placebo and standard iron supplementation groups. Porter found compliance with iron supplementation in antenatal patients given a single daily dose to be 94% compared to 62% in those assigned a thrice daily preparation. Similar findings have been observed in studies of anti-tuberculosis medications, where 10% more patients were adherent to a single trivalent drug in comparison with those receiving the same three medications as separate preparations (Sbarbaro). Lobel, Carme and Hoebe present data on daily compared with weekly anti-malarial regimens. Lobel found reported compliance with weekly and semi-monthly regimens of mefloquine to be slightly better than weekly chloroquine (95% and 94% vs. 90%, respectively) and much better than the 70% compliance with the twice daily regimen of primaquine. Carme found reported compliance during travel to be similar (99%) in those receiving weekly mefloquine and daily chloroquine and proguanil. Hoebe found that those taking a weekly regimen of mefloquine reported lower regimen rejection rates (i.e., never initiated regimen) than those taking a twice daily regimen of proguanil, 5% vs. 9%, respectively, and had greater overall compliance, 74% vs. 64%.

Multiple daily doses and complicated dosing are sometimes promoted to improve absorption and utilization, and ergo effectiveness, but are associated with poorer compliance (i.e. incomplete and incorrect adherence). An exception to this is the promotion of weekly or semi-weekly iron supplementation. Evidence from animal studies clearly indicates better absorption of supplemental iron on a less frequent periodic than daily basis (Viteri), however studies in humans are more equivocal, showing similar effectiveness of daily and weekly iron supplementation (Cook). The evidence regarding daily compared with weekly supplements is not strong. Most nutritional supplementation studies give daily placebos to those receiving weekly regimens to blind their participants to their assigned regimens and thus reduce respondent bias. The best examples of daily vs. weekly regimens are found in studies of anti-malarials, but these comparisons of compliance may be confounded by side effects.

Figure 1:
Compliance and Frequency



Duration of regimen

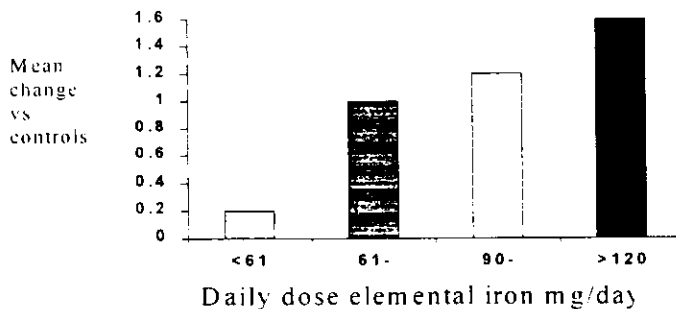
Increased duration of regimens has been consistently associated with higher discontinuation of the regimen and reduction in compliance (Cramer, Potter, Sbarbaro). In pregnant women receiving daily or weekly iron supplementation, Ridwan found compliance was 67% in pregnant women prior to 12 weeks of supplementation and declined to 44% thereafter. Similarly, Hemminki found 75% of women taking routine daily iron supplementation were compliant at their second study visit (around 28 weeks gestation) and declined to 63% at their third visit (around 36 weeks gestation). Potter found the 90%, 89% and 83% compliance of women taking oral contraceptives, measured by MEMS, over their first, second and third monthly cycles. The percentage of women who took 100% of the oral contraceptives during their first and third monthly cycles was 33% and 19%, respectively. Women who missed more than two pills increased from 31% during cycle 1 to 51% during cycle 3. Rosenberg found 60% of European women stopped taking oral contraceptives within two years of initiation. Potter found 20% of Colombian women stopped taking oral contraceptives within four weeks of initiation. Compliance with anti-malarial prophylaxis also demonstrates decline over time. Croft found reported compliance with mefloquine to decline from 85% at two weeks to 69% at eight weeks; chloroquine and proguanil compliance declined from 89% at two weeks to 68% at eight weeks. Carne found reported premature termination of prophylaxis (discontinuation prior to two weeks return from travel) to be 13% in those taking mefloquine and 4% in those taking chloroquine. Hoebe also reported premature termination of prophylaxis in 16% of those taking mefloquine and 25% of those taking chloroquine.

Dose

Salway found continuation rates with low dose oral contraceptives to be greater than standard dose users. 11.4 vs. 9.3 months, respectively in Matlab, Bangladesh. This difference may not be attributable to dose per se, but rather to initiation of a new product (the low dose pill) in the area.

Dose does not appear to be directly related to compliance. As noted above, compliance appears to be greater with weekly than daily doses. Dose is, however, directly related to effectiveness (Sloan), although periodic supplementation generally provides lower overall doses than daily supplements. Dose is also theoretically associated with perceived side effects (discussed below). For this reason, slow release (GDS) iron supplementation formulations were developed. GDS supplements containing 50 mg elemental iron are estimated to have greater absorption and are therefore similar to 100-120 mg standard ferrous sulfate formulations. Ekstrom found better compliance in the GDS than control (standard iron) group, but this is possibly due to the difference in the frequency of the regimens (GDS 1/day; control 2/day, one morning and one evening dose). Simmons found similar compliance, around 90% as assessed by pill count, in those receiving GDS, standard iron, and daily placebos (all women received daily folate supplementation as well). Lobel found little difference, 95% vs. 94%, in reported compliance of those taking the 250 mg mefloquine once a week or bi-monthly, although the weekly dose constitutes double the bi-monthly dose.

Figure 3: Iron supplementation & anemia reduction by dose



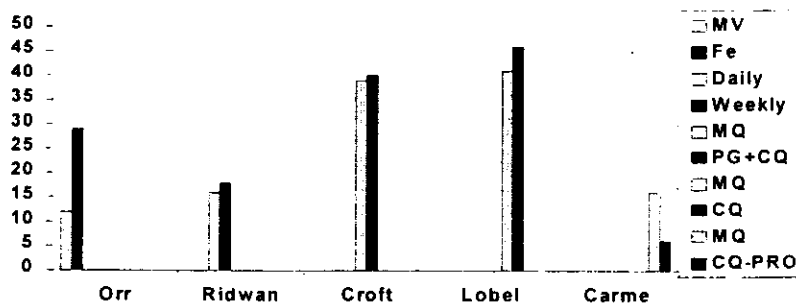
Source Sloan

Side Effects

Side effects, including unappealing taste, odor, and physiologic effects of medications, have been blamed for non-compliance. Two hundred years ago Moliere wrote "most men die of their remedies and not of their illnesses". In fact, side effects do not consistently or greatly differ between those receiving placebo, lower and higher doses (Sbarbaro). An exception to this may be iron supplementation. Simmons found similar side effects in pregnant women receiving placebo, ferrous sulfate and attributed the side effects to discomforts of pregnancy rather than iron supplementation. However, in northeastern Thailand Charoenlarp found 30% of those taking 240 Fe/day prenatal iron supplements and 10% of those taking 120 Fe/day to report side effects. In a meta-analysis Scholl found perceived gastro-intestinal side effects were related to dose (Scholl). Sbarbaro and Simmons point out the real problem with perceived side effects is that they are attributed to the regimen by those taking the prophylaxis or treatment. The greater

reported side effects are the lower the compliance is with the regimen. Ekstrom found reported side effects reduced compliance with antenatal iron supplementation from 61% to 44% in the GDS group and from 42% to 30% in the standard preparation group. Ridwan found overall compliance with iron supplementation to be 64% in those without side effects and 21% in those with side effects. Rosenberg noted side effects were the most common reason given for discontinuation of oral contraceptives; 51% of women experienced side effects associated with oral contraceptives in his study. Hoebe found 53% and 24% of non-compliance was attributed to side effects associated with mefloquine and proguanil, respectively.

**Figure 3:
Compliance & Side Effects**



Beyond this, there is no clear pattern of side effects by type of regimen. Anti-malarials and iron supplementation appear to have the most common reports of side effects. Orr found fewer side effects in those taking daily multivitamins than daily iron supplementation, 12% vs. 29%, respectively. Reported side effects with different formulations of iron supplementation generally range from about 15% to 30%. Iron supplementation given with meals or in smaller doses over time is associated with a reduction in perceived side effects but is also associated with a reduction in effectiveness (presumably due to poorer absorption). GDS has been shown to reduce perceived side effects (Cook, Ekstrom), but not consistently (Simmons). A much broader range, 2% to 75%, of side effects is reported by those using anti-malarial prophylaxis. While some of the reviewed studies indicate more side effects with mefloquine than chloroquine prophylaxis, others show just the opposite. The one consistent finding is that those taking mefloquine report more neuropsychological side effects and those taking chloroquine report more gastrointestinal side effects (Carme, Croft). Positive effects of prophylaxis and treatment are generally perceived after termination of the regimen, while negative (side) effects are commonly reported during the regimen. Side effects are generally reported to diminish over time, although some studies of mefloquine prophylaxis indicate an increase in perceived side effects over time.

Perceived importance

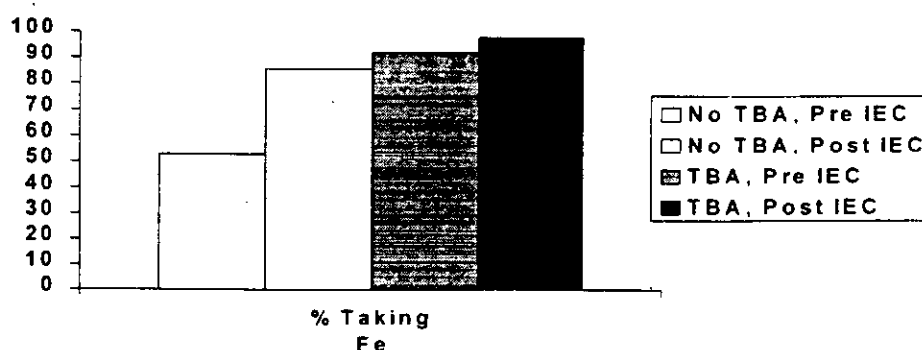
It has been argued that understanding the importance of the prophylaxis or treatment and the severity of the condition being prevented or treated affects regimen compliance. Substantial evidence exists however to indicate that compliance is, at best, weakly associated with the patient's perception of the importance of the prophylaxis or treatment or with the severity of disease prevented or treated (Cramer, Sbarbaro, Wright). Non-compliance with regimens is common in epileptic patients, even though they recognize the danger of non-compliance and severity of the consequences of non-compliance, including seizures without advance warning that may result in serious physical harm and job loss (Cramer). Post-operative patients with life-threatening heart disease have been observed to reject their medications at their bedside, prior to hospital discharge (Cramer). Potter found 83% of women who used oral contraceptives correctly perceived them as crucial to preventing pregnancy, however nearly as many women, 78%, of those who used oral contraceptives incorrectly had the same perception. Hoebe found 7% of those given mefloquine and 5% given chloroquine thought the anti-malarial prophylaxes were useless.

Information/comprehension of correct regimen

Counseling patients on the importance of the prophylaxis or treatment and on how to take the regimen correctly is consistently promoted (Cramer, Harper, Sbarbaro). Clearly patients cannot take therapy correctly unless they are informed how to do so. Orr found that 1% and 22% of those taking multivitamins and iron supplements, respectively, knew the correct dose but took less. Of those who knew the purpose of iron supplementation, Schultink found only 75% took them; additionally 25% who did not know the purpose took the supplements. Rosenberg found significant associations between not taking oral contraceptives at the same time every day and not understanding or reading instructions on taking oral contraceptives. He also found missing consumption and discontinuation of oral contraceptives to be associated with not receiving adequate information or help from a provider about side effects. Unfortunately, these associations may not necessarily be ameliorated by provision of information or counseling; this requires further evaluation.

Counseling has been shown to improve short term compliance, but the benefits are poorly sustained over time (Sbarbaro). A quasi-experimental study carried out in rural Indonesia showed an increase in the proportion of women taking prenatal iron associated with an intensive educational campaign (53% to 86%) that stressed the importance of iron-folate supplementation, how to take the supplements correctly, how to deal with the side effects and where to obtain the supplements. The effort was costly, however, and the campaign's effect was nearly null (increased from 92% to 98%) in the presence of TBA community-based distribution of iron tablets (Utomo). Improving provider-patient interaction and special follow-up reminders have been heavily promoted (Cramer, Galloway, Sbarbaro, Wright). These mechanisms seem to improve patient satisfaction, however they have not been adequately tested and long term compliance has not been found to be related to initial physician-patient interaction (Cramer, Sbarbaro).

Figure 4: Information & Iron Taking Behavior



Source: Utomo

Availability

The availability of supplies is crucial to obtaining pills and supplements for consumption. It has been suggested that the lack of availability is the greatest hindrance to iron-folate supplementation programs (Gillespie). Schultink found 15% of pregnant women took less than two-thirds of their iron supplementation and all of these women claimed that there had been no resupply. Potter found 6% of non-compliance was attributable to oral contraceptive supplies running out. In a controlled intervention study in Indonesia, making iron-folate tablets available by having traditional birth attendants distribute them to pregnant women in the community resulted in 40% more women consuming iron-folate supplements than pregnant women in a nearby area who could only obtain the supplements from prenatal clinic (Utomo). While this study showed women in the TBA distribution area consumed approximately eight more tablets than women in the control area, their self-reported monthly consumption was <50% of the supplement regimen. Similarly, improving access of therapeutic regimens by providing them at the work site has been shown to improve compliance (Alderman). While lack of supplies limits pill taking, Simmons recognizes that after the elimination of procurement and distribution problems, other problems affecting compliance (particularly the perception that side effects are attributable to iron supplements) will again emerge as the major difficulties for supplementation.

Appearance/packaging

It has been proposed that the appearance and packaging of pills supplements affects pill taking behavior (Cramer, Galloway, Potter). This seems probable where ambient conditions affect the integrity of the pill. Early trials of MSG fortification found the formulation became yellow and clumpy, and resulted in reduced purchase and consumption (Murphy). Low compliance with iron-folate supplementation has been attributed to poor storage of iron tablets resulting in tablet disintegration, stickiness or metallic or tannic flavor in Indonesia and Thailand (Charoenlarp,

Moore). Special packaging and pill formulation (color, coating) has been promoted to improve pill taking. Correct consumption of oral contraceptives has been found to be improved in packages of 28 (continuous) daily pills as opposed to packages of 21 daily pills with a seven day interim rest from pill taking (Rosenberg). Blister packs have been proposed to improve compliance with iron supplementation. The relative cost of such packaging may be prohibitive for public health delivery systems and therefore may not be a useful approach. If the cost of special packaging and pill formulation limits the availability of the supplements, the compliance with and effectiveness of the available supplements would have to be proportionately greater to compensate for the amount of supplements unavailable due to cost. For example, if women could only receive half of the special regimen supplements (due to a doubling of cost), the compliance with and effectiveness of the supplements would have to be double that of the normal formulations/packaging to have equivalent effect. Otherwise, targeted delivery systems involving identification of target individuals or areas, which in themselves are more costly and logistically difficult than general public health delivery systems, would need to be implemented to effectively reduce nutritional deficiency. As the extent to which special packaging and formulation of supplements can improve compliance is unknown, a controlled field trial of the compliance with and effectiveness and costs of specially packaged formulations needs to be tested before special packaging and formulations are promoted.

Cost

It has been suggested that the cost of medications limits their availability to patients. While this is certainly true when costs of prophylaxis or therapy are not affordable, there is little evidence that the removal of patient fees or costs of medication improves adherence (Sbarbaro). The increased cost of vitamin A fortified sugar initially delayed this effort in Guatemala (Arroyave). Conversely, it has also been suggested that the imposition of fees for service improves their utilization. Arguments have been made that structural adjustment policies have resulted in diminished utilization of services that might affect consumption of medication, however evidence regarding the benefits of imposing fees for service is also scant (Galloway).

Forgetfulness

One factor that is consistently pointed out as a cause for non-compliance is forgetfulness (Cramer, Sbarbaro). Potter found 6% of those taking oral contraceptives claimed they simply forgot to take the pills on occasion. Hoebe found 17% of those on anti-malarial regimens forgot to take the pills. Third party responsibility for regimen provision has been proposed to increase compliance (Sbarbaro). Supervised consumption appears to improve compliance (Charoenlarp).

Determinants of Compliance Summary

Lack of regimen adherence in pill-taking behavior is a large problem. Self-reported reasons and provider perceptions don't always accurately reflect the reasons for non-compliance or discontinuation and much non-compliance remains unexplained (Ekstrom). Theories abound regarding the determinants of pill taking behavior and compliance, but few of these theories have

been adequately tested to determine what interventions can actually improve compliance. It is clear that regimen simplicity and regularity improve compliance. Availability of supplies is also critical. Whether, and to what, extent pill taking behavior can be improved by modifying other factors statistically or theoretically associated with compliance requires further investigation.

Considerations for Maternal Micronutrient Supplementation in Developing Countries

There are a number of important considerations to take into account prior to the development, promotion or implementation of maternal micronutrient supplementation strategies in developing countries.

Program Goals: The first consideration is the purpose of the supplementation program: is the goal of the program to reduce maternal mortality, maternal morbidity or simply to reduce nutrient deficiency?

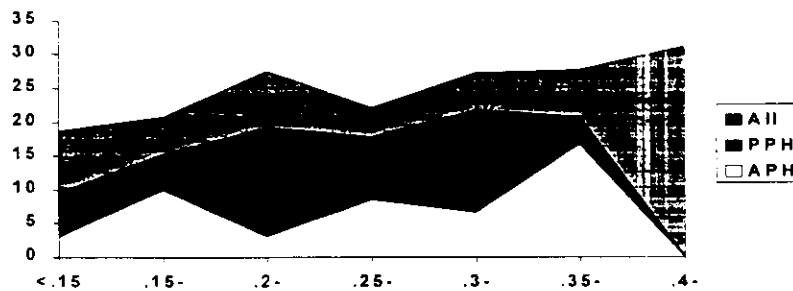
Supplement Efficacy: Efficacy, that is the ability of the supplement to impact on the outcome of interest (maternal mortality, morbidity or nutrient deficiency) under ideal circumstances, is usually measured through randomized controlled trials. The supplement must be shown to have an efficacious impact on the outcome before it's promotion for that purpose. It is important to review the evidence to be sure the supplement is efficacious to avoid implementing ineffective large-sweeping programs with the idea of potentially reducing maternal mortality or morbidity.

Vitamin A supplementation has been demonstrated to reduce maternal mortality in Nepal (West). This study's findings meet all of the criteria used to determine the causality of a relationship (described below), including consistency with findings from numerous studies of vitamin A supplementation in children (Barclay, Hussey, Ramathullah, Sommer, Vijayaraghavan, West). Replication studies of the effects of vitamin A supplementation on maternal mortality are being designed. The mechanisms by which vitamin A supplementation reduces maternal mortality are unknown, but are theorized to be related to the reduction of the severity of infection and improvement in tissue integrity.

Iron supplementation is efficacious in improving hematologic indices and reducing maternal anemia, but no data exist on the effects of maternal iron supplementation (as prophylaxis or treatment) to reduce maternal mortality (Rush, Sloan). Some data indicate that maternal mortality is associated with anemia (Llewelyn-Jones), but the causality of this relationship is questionable. Women with more severe anemia are likely to be poorer than non-anemic women or women with less severe anemia. Due to their poverty, they may also be less likely to present themselves for delivery in an institution in a timely manner (or at all). While all women may be at similar risk of experiencing an obstetric emergency, poor women, who are more likely to be malnourished and severely anemic, are less likely to receive timely medical management for life-threatening obstetric conditions and are therefore more likely to die from these conditions than better off women. Other data indicate that there is little relationship between anemia and

maternal mortality (Harrison). The presumption that anemia is a major contributor to maternal death is based on the theories that anemia leads to oxygen starvation, depressed immune systems, and increases the risk of death in women experiencing hemorrhage. These are plausible reasons, but they remain theories with inadequate supporting data. The data do not indicate that anemia contributes *causally* to maternal mortality or that alleviation of anemia through supplementation prevents maternal mortality. Women experiencing hemorrhage do not require immediate supplementation, nor is there evidence that supplementation would have reduced their risk of death; they require obstetric services to reduce the bleeding and to replace blood loss. Replacement of blood loss and avoidance of shock in women experiencing postpartum hemorrhage has been shown to prevent maternal death (Chalmers). Iron supplementation has been demonstrated to impact on physical productivity, but its relationship to maternal morbidity beyond this is unclear (Bothwell).

**Figure 5:
Maternal mortality by hematocrit**



Source: Harrison

Calcium appears to be efficacious in reducing pregnancy-induced hypertension and pre-eclampsia (Carroli, Guyatt) and osteoporosis (Shils). Zinc supplementation appears promising for the reduction of maternal infection (Shrimpton, Yip). Iodine supplementation reduces goiter and congenital cretinism (WHO). Prenatal folate supplementation reduces neonatal neural tube defects (Shils).

Supplement Effectiveness: After obtaining evidence regarding the efficacy of the supplement and before promoting supplementation programs, the effect of the supplement on the outcome of interest must be demonstrated under different conditions through field trials using contemporaneous comparison groups. These evaluations must meet the criteria to determine whether the effect is causal (Mausner, Susser). These criteria, which are applicable to both studies of efficacy and effectiveness, are:

1. Temporality of events: Consumption of the supplement must occur prior to the effect (reduction of maternal mortality, morbidity, deficiency);

2. Strength of the effect: The larger the effect the greater the likelihood the factor is causally associated with the outcome;
3. Dose-response relationship: The likelihood of a causal relationship is strengthened when a gradient of effect across supplement dose is demonstrated;
4. Consistency of the association: The associations detected in various studies conducted under different conditions and with different populations show effects that are consistently in one direction (i.e., consistently show a *reduction* in maternal mortality, morbidity or deficiency). This is a critical criteria to determine the effectiveness of field programs that are often difficult or costly to evaluate by randomized controlled trials; under such conditions, quasi-experimental studies are often conducted (Fisher).² The magnitude of the effect of a nutritional supplement, however, would be expected to vary in populations with different levels of nutrient deficiency or concomitant factors that affect the relationship between the supplement and it's effect (for example hookworm infection affects iron deficiency).
5. Biologic plausibility of the relationship: This is an additional criteria that lends support to determining whether a relationship is causal. It is important that the biologic means by which a nutrient is theorized to reduce mortality, morbidity or deficiency *is not in contradiction* to (i.e., is coherent with) current knowledge. The utility of this criterion depends upon the current state of scientific information, which may be little or incorrect. Therefore, this is not a mandatory criteria to determine causality.

The NNIPS-2 study of the impact of vitamin A supplementation in pregnant and postpartum women was a large randomized controlled trial, but was analyzed by "intent to treat". This means women who were not fully compliant with supplement's regimen were included in the analysis of effectiveness. Although the magnitude of the reduction in maternal mortality cannot be construed as generalizable, because supplements were delivered on a weekly basis by study team household visitors and supplement consumption was observed, the study does not simply represent the efficacy as observed under ideal conditions. Compliance with the supplement's regimen was >80% taking at least 50% of the regimen's supplements or an overall compliance of >40% (K. West, personal communication).

In the past forty years, much emphasis has been placed on maternal anemia. Anemia is the most common nutritional deficiency in the world, and is most prevalent in pregnant women. WHO estimates that approximately 60% of women in developing countries suffer from anemia (<11 g/dl) and 7% have severe anemia (<7 g/dl). It has been argued that iron supplementation is cheap and effective in reducing anemia and women's risk of death. Yet, the effectiveness of iron supplementation programs has been equivocal, and the prevalence of global maternal anemia has remained virtually unchanged in the past thirty years, even in the presence of national and

² Recent promotion of program evaluation without contemporaneous control groups has been promoted (Campbell, Ronsmans) on the basis that no control group is perfect. This recommendation ignores the foundation of social science and epidemiology and inaccurately infers that causality can be determined from uncontrolled pre-post assessments. No single control group or study can confirm a causal relationship; the determination of a causal relationship must include and meet the criteria of consistency across studies.

regional clinic (prenatal) and community-based iron supplementation programs. Part of the reason for this lack of success is that these programs have not overcome many of the obstacles to making iron supplements available to all pregnant women. Poor absorption of the supplements and poor compliance with available iron supplementation contributes to the problem. Studies have shown that community-based distribution approaches are more successful than clinic-based approaches in terms of iron consumption because they increase the availability of supplements. The efficacy of prenatal iron or iron-folate supplementation on reducing anemia is dose-related. Iron supplementation is often initiated in the last three months of pregnancy, and due to the short duration of supplementation, has limited potential alone to reduce maternal anemia.

Additionally, not all anemia is caused by iron deficiency (Scholl). Anemia may be caused by many things, including poor diet (iron, folate, vitamin B12), impaired absorption, blood loss (menstruation, childbirth, hemorrhage), chronic infection (malaria, hookworm infections), genetic conditions (thalassemia and sickle cell) and metabolic disorders. Although iron supplementation may temporarily improve hemoglobin levels, it is unlikely to resolve anemia due to other causes. Treatment of malaria and hookworm infections is efficacious in reducing anemia (Sloan). Treatment of malaria for pregnant women is extremely important as women can die of malarial related seizures during delivery. Vitamin A supplementation alone has been shown to be efficacious in improving hematologic status (Stolzfus, Suharno), and very efficacious in combination with iron supplementation. Prevention of malaria saves women's and children's lives (Binka). A variety of prevention strategies have been proposed including sleeping under treated bednets has been shown to be efficacious. Hookworm disease can be prevented by wearing shoes or preventing soil contamination (by building and using latrines and animal pens for example). The effectiveness of antimalarial prophylaxes to reduce anemia has been ambiguous, and the effectiveness of hookworm prevention and vitamin A supplementation programs on maternal anemia requires further investigation.³

It is questionable whether the efficacy of calcium supplementation on pregnancy induced hypertension, which is thought to be a major contributor to maternal mortality, requires further investigation. The effectiveness of calcium supplementation, however, needs contemporaneously controlled field evaluation (Yip). The efficacy of zinc supplementation needs to be established prior to initiating studies of its effectiveness. Global iodine deficiency is effectively being prevented through salt fortification (WHO).

Supplement effectiveness and dose: How much is enough?

Interestingly, doses far below daily recommendations have been shown to be efficacious in reducing maternal mortality and morbidity. One reason for this may be that the efficiency of the

³ These studies will need to account for the gestational effect of hemodilution (i.e., the increases in women's blood volume without a proportionate increase in the number of red blood cells that occurs over pregnancy). This hemodilution results in a decline of hemoglobin levels from the 20th to the 35th week of pregnancy after which fluid volume stabilizes and hemoglobin levels increase. Not accounting for the gestational effect of hemodilution has confounded many of the past studies on the effects of iron supplementation on maternal anemia.

absorption and utilization of nutrients is increased in deficient individuals, unless they concomitantly suffer from other conditions that limit their absorption (particularly infections). Another reason may be that the recommended daily allowances for all nutrients except calories are sufficient to cover the estimated nutrient needs of 97.5% of a healthy population (NAS), and therefore exceed the needs of 47.5% of most of the population. Olson has suggested that the lower international recommended daily intakes are more appropriate than the higher American recommended daily allowances.

In conjunction with (or as part of) the needed future studies on the effectiveness of micronutrient supplementation, attention needs to be paid to dose-response to determine if there is a minimum threshold beyond which effectiveness is minimal. This information is useful to select the lowest dose with greatest effect that may be provided by periodic delivery systems. Periodic delivery systems are cost-effective and affordable ways to provide multiple doses to be taken over time on a single occasion (discussed below).

Delivery systems and minimizing program costs:

Feasible and affordable delivery systems need to be identified and evaluated to determine the extent to which they can safely and effectively provide micronutrient supplements to the target population. Food fortification has been a successful long-term delivery system for improving nutritional status in the United States and Europe. It is the main approach used to safely improve women's iodine status and prevent goiter and congenital cretinism (WHO). Fortification of foods and condiments with other micronutrients has been attempted in developing countries (Sommer) and found to be efficacious in reducing deficiency, but can be problematic to implement on a large scale in non-industrialized countries (McLaren, Sethuraman). Dietary modification is another long-term approach to improving nutritional status, but is dependent on many factors and has had qualified and variable levels of success (Willett).

Periodic distribution of micronutrient supplements remains an important short to medium term strategy due to the delivery systems' affordability and implementation feasibility. WHO and OMNI have suggested micronutrient supplements may be provided to women at prenatal care visits, delivery or first postpartum contact, and through child immunization and supplementation programs (WHO). These modes of delivery can be useful for provision of multiple daily or weekly supplements (to provide the amount of supplements necessary to cover monthly, quarterly or semiannual needs) or for periodic delivery of single megadose supplements (such as for child or postpartum vitamin A supplements).

Special precautions need to be taken before recommendation or implementation of micronutrient supplementation programs, however. Unlike vitamin A supplementation for children or postpartum women, periodic delivery of megadose iron, calcium and zinc is contraindicated as these nutrients may be toxic if consumed in excess pregnant women and by children or adults (Rosso, Shils). Excess intake of vitamin A and vitamin A deficiency in pregnant women can be teratogenic (Bendick, Hathcock, Olson). Overcompliance and excess intake is generally limited

to the period in which supplementation is initiated (Ekstrom) although "making up" for missed doses is chronic with oral contraceptives (Potter).

Excess intake, while generally limited to the period in which supplementation is initiated (Ekstrom). Overcompliance, when measured, has been consistently observed in pill taking behavior (Cramer, Ekstrom). Overcompliance must be considered to avoid the excess intake that can occur when providing women with more than a single dose (i.e., a monthly, quarterly or semi-annual supply). For example, women's vitamin A status might best be improved by providing vitamin A supplementation to non-pregnant women of reproductive age because vitamin A is a fat-soluble vitamin that can be stored in the liver for future use. This could avoid the risk of teratogenicity, except that pregnancy is often undisclosed and frequently unrecognized (even by women themselves) in early gestation and therefore identifying women who truly are not pregnant is not simple or straightforward. Therefore, except for postpartum women within 60 days of delivery, women must be provided with multiple lower dose supplements to avoid excess intake in pregnancy.

Periodic distribution systems, whether community-based or clinic-based, are cost-effective ways of providing micronutrient supplements because they minimize the costs of the most costly component of supplementation programs, the distribution system. While the cost of the supplement is a factor for consideration, it has been found to be a minor factor in the costs of nutritional supplementation programs compared to the costs of the delivery system (Fiedler, Sanghvi). The proportion of the supplementation program attributable to the cost of the supplement will be greater for maternal supplementation than for vitamin A supplementation of children because women of reproductive age whose non-pregnancy status is unverified cannot receive single megadose supplements every few months. These women must receive multiple daily or weekly lower doses of micronutrient supplements.

There are a number of ways to minimize the costs of nutritional supplementation programs while assuring that effective doses are provided in a manner in which they will be consumed safely. Ensuring that women take the supplements correctly is problematic. Although studies in developed countries have found little association with pill taking behavior and education, little is known about illiteracy and incorrect pill taking behavior and incorrect pill taking behavior is common among those who are not illiterate (Cramer, Potter, Sbarbaro).

Supplements can, however, be provided in a manner that does not threaten the safety or effectiveness of the supplement, regardless of poor pill taking behavior. For example, 30 daily doses of 5,000 IU vitamin A can be provided through clinic- or community-based distribution systems to all women of reproductive age. West found a 43% reduction in maternal mortality associated with >40% compliance with weekly doses of 25,000 IU vitamin A (consumption of about 10,000 IU per week). Currently, recommended daily doses of vitamin A are 10,000 IU (NAS) and 8,000 IU (IVACG). A daily dose of 5,000 IU is equivalent to 35,000 IU per week. In addition, because vitamin A is a homeostatic, lower doses of vitamin A supplementation should be utilized more efficiently in deficient populations and may achieve similar response to higher doses in less deficient populations. Providing multiple daily doses of vitamin A would cost six

times more than providing weekly supplements. Yet the cost of the supplement is mostly in its formulation (capsule, tablet, etc) and packaging rather than in the cost of the nutrient. Formulations that are stable, safe and acceptable may reduce the costs of the supplements to the extent that the cost differentials between weekly and daily supplements would be miniscule (West). Compliance with weekly regimens is generally somewhat better than with daily regimens, but effectiveness of both appears similar. This may be dose related as missing a daily dose once a week is equivalent to missing 14% of the regimen whereas missing one weekly dose in a month is equivalent to missing 25% of the regimen.

Combining micronutrient supplements has been promoted to simultaneously alleviate multiple deficiencies and to reduce supplementation program costs, as much in the delivery system as in the supplement formulation itself. This has been the typical approach in combining prenatal vitamin and iron supplementation in the US and Europe. The biologic interaction of specific nutrients needs to be taken into account where micronutrient supplements are combined, either in a single formulation or in a single delivery system with multiple formulations. For example, zinc enhances vitamin A metabolism, vitamin A may improve iron utilization, iron and calcium inhibit each other's absorption (Shils, Stoltzfus, Suharno). The program purpose and the efficacy and effectiveness (including the effect of compliance on effectiveness) in serving the program's purpose needs to be examined when combining micronutrients. If reduction in maternal mortality and morbidity is a primary purpose of the program, prioritization should be placed on vitamin A and calcium supplementation (the latter to reduce pre-eclampsia and related mortality). Small studies should also be conducted to determine the effects of combining micronutrients on compliance and biologic response to permit selection or exclusion of nutrients from the combination depending on program priorities, observed compliance with complex combinations compared to simpler (single or limited combinations of) nutrients.

The frequency and mode of distribution may also reduce costs. The more infrequent the distribution system is, the less expensive and more feasible it is to implement. Regimen adherence appears to diminish over time, regardless, and may not be affected by small differences in the periodicity (monthly, quarterly, semi-annually) of supply distribution. Integration of services including the distribution of supplements through prenatal care, obstetric care, postpartum care, neonatal, infant and child care, family planning and other nutritional supplementation programs may be effective and reduce program costs. Integration of services can be accomplished at the community or clinic level. Women's use of this integrated care system can be initiated at any stage of the reproductive cycle, between pregnancies with family planning, during pregnancy with prenatal care provided by the TBA or nurse-midwife, or postpartum with maternal and/or infant care. Integration of these services can even begin through child vitamin A supplementation or immunization campaigns. While integration of these services is theoretically a good idea to improve overall utilization of health services, the feasibility, costs and acceptability of these combinations of services should be assessed before integrating the services on a large scale to ensure that the integration of one service is not detrimental to the other. For example, integrating vitamin A supplementation with prenatal iron-folate supplementation may reduce the acceptability of and compliance with vitamin A supplementation because women may attribute the perceived side effects of iron to vitamin A.

Similarly, integration of vitamin A supplementation with family planning programs might reduce the acceptability of vitamin A supplementation where contraception is not well accepted. Conversely, the integration of family planning programs into vitamin A supplementation programs might improve the formers acceptability.

Targeted distribution may also reduce program costs. Targeting individuals is generally impractical: this requires the ability to accurately diagnose or screen individuals. There is some indication that self-reported night blindness is a useful indicator of women with vitamin A deficiency in some countries (West). This indicator may avoid much false overdetection of women who are not deficient.⁴ Self-reported night blindness, however, will not detect those cases with vitamin A deficiency that do not manifest themselves through night blindness, including those with less severe deficiency who may nevertheless benefit from supplementation. Beyond this indicator however, inexpensive means (self-reported symptoms, dietary assessment) to identify micronutrient deficiency in individuals is very inaccurate (Rush, Sloan, Willett). Even relatively inexpensive biochemical methods for identifying micronutrient deficient individuals is problematic (Willett). Using biochemical measures to accurately targeting individuals attending prenatal clinics is still economically, and sometimes technologically, infeasible for many developing countries. Identification of ocular manifestations of vitamin A deficiency is possible and inexpensive if conducted at the clinic level, but will miss many women with less severe forms of vitamin A deficiency. Identification of women with pregnancy-related hypertension is also possible and affordable at the clinic level. Beyond this, affordable means to accurately identify individual women with micronutrient deficiency are not currently available.

Identification of populations with high prevalence of micronutrient deficiencies with inexpensive methods may be possible. To date, these methods have shown the ability to identify communities where most of the deficient cases exist, but at the cost of misclassifying a substantial number of communities where the deficiency is not on the order of a public health problem (Sloan). Micronutrient supplementation programs could be initiated in these communities and would provide supplementation to most of those who need it, but would also provide supplementation to many misclassified communities with few deficient individuals. The cost of using simple dietary screening methods to identify communities where more than 15% of the women have specific micronutrient deficiencies should be investigated before using such methods to identify target populations. Communities or regions where micronutrient supplementation programs should be implemented may be selected on the basis of children's micronutrient programs, using children's level of deficiency as a surrogate measure for mother's level of deficiency. Vitamin A deficiency is a clustered phenomenon (Sommer), and micronutrient deficiency is likely to be occur in adults where adults and children share common diets and children are deficient. This appears to hold true for anemia (Tanumihardjo).

⁴ At least until treatment is given for this condition. Once women recognize they can get free medication if they report themselves to be night blind, they may falsely report their condition.

Perhaps the most feasible approach is to identify countries and/or regions within these countries where the micronutrient deficiency is common. Identification of countries with maternal vitamin A deficiency and anemia is probably unnecessary, as substantial information exists on the global occurrence of children's vitamin A deficiency and maternal anemia. Maternal vitamin A deficiency is most likely to occur in countries where vitamin A deficiency is (or would be if it were devoid of supplementation programs) common in children. Iron deficiency, however, requires further identification in countries where maternal anemia is common to determine the extent to which the prevalent anemia is attributable to iron deficiency, and to what extent iron deficiency is the primary cause of that anemia. For example, most anemia in the country of interest may be found to be iron deficiency, but with hookworm infection or malaria as the primary cause. Under these conditions, the alleviation of iron deficiency anemia may be best and least expensively obtained through hookworm and malaria control programs. Indeed, cottage industries to make and sell shoes may result in reducing hookworm disease (coupled with an initial treatment program), improving the community's economic status and diet, thus reducing not only anemia but other nutritional deficiencies. Targeting vegetarian populations may also be a relatively inexpensive way to identify women who are likely to have iron deficiency anemia. This alone, however, is not sufficient as much iron deficiency probably occurs in other populations as well. Sample surveys may be the best means to identify countries or regions where zinc deficiency is common, however large scale surveys may be unwarranted until more evidence is available regarding the efficacy of zinc to reduce maternal morbidity and/or mortality. Low dose calcium supplementation may best be targeted to pregnant women to reduce pre-eclampsia.

Targeting population groups, in this case pregnant, postpartum and lactating women, for supplementation may also be a cost-effective approach to reduce maternal micronutrient deficiency. Targeted duration of supplementation will also reduce costs and maximize effectiveness. One of the few things known about compliance with pill taking is that it diminishes over time. This strategy limits the duration of supplementation to the period in women's lives when the demand for these nutrients is greatest and when supplementation has its greatest life-saving potential. This will result in approximately 7.5-12 months (the last 4.5-6 months of pregnancy when most pregnancies are identifiable, plus 3-6 months postpartum) maternal supplementation per pregnancy. For this to be a cost effective approach, the cost of identifying women during pregnancy, at delivery or during the early postpartum period must be offset by the reduction in cost from universal and continuous maternal supplementation. Such identification may be achieved inexpensively through prenatal, postpartum, child and other reproductive health programs (including community based family planning distributors). Integration of micronutrient interventions has also been promoted as a potentially cost-effective way to improve women's health and save women's lives. The integration of health services should be carefully investigated before strategies are promoted on a large scale. Integrating prenatal vitamin A supplementation with ongoing prenatal iron supplementation programs may reduce the acceptability of and compliance with vitamin A supplementation as women may believe vitamin A supplements will have the same side effects as iron supplements. Similarly, integration of vitamin A supplementation with family planning programs might reduce the acceptability of vitamin A supplementation where contraception is not well accepted.

Conversely, the integration of family planning programs into vitamin A supplementation programs might improve the latter's acceptability in areas where the benefits of maternal or child vitamin A supplementation are perceived even if there is little existing contraceptive use. Further investigation to determine where integration takes precedence over prioritization of services needs to be conducted to clarify the potential benefits and detriments of combining services and the severity of the consequences in the absence of individual services.

Conclusions

This paper has described what is known about pill taking behavior and its implications for micronutrient supplementation for safe motherhood. Lack of adherence is a large problem that reduces the effectiveness of the regimen. Regimen simplicity, regularity and availability of supplies improve compliance. Self-reports and provider perceptions do not accurately or completely reflect the reasons for non-compliance or discontinuation. The extent to which pill taking behavior can be improved by modifying factors statistically or theoretically associated with compliance requires further intervention, rather than descriptive, research. Modification of these factors should be implemented and contemporaneously controlled investigations should be conducted to assess the effects of the modifications.

The purpose of programs implementing maternal micronutrient supplementation need to be identified during the program planning stage to select appropriate interventions. Programs attempting to reduce maternal mortality through micronutrient supplementation should currently focus on vitamin A. The effectiveness of these interventions needs to be tested prior to their implementation as large scale programs. Programs attempting to reduce maternal morbidity should currently focus on calcium supplementation. The extent to which global and regional anemia is caused by iron deficiency needs further investigation. Alternative mechanisms to alleviate iron deficiency, by iron supplementation, hookworm treatment and prevention, and antimalarial treatment and prophylaxis should be investigated. Zinc supplementation is promising but requires further investigation to determine its benefits for safe motherhood.

Once sufficient information exists about the efficacy of micronutrients to reduce maternal morbidity and mortality, further research needs to be conducted to identify feasible, affordable, safe and effective means of providing micronutrient supplements to pregnant, postpartum and lactating women. These investigations should determine the benefits and detriments of different delivery systems, including the combination of micronutrients and integration of services.

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Table 1 Acronyms

CQ: Chloroquine
d: Day
int.: Intervention
H-H: House-to-house
gest: Gestation
GDS: Gastric delivery system
MQ: Mefloquine
MRDR: Modified relative dose response
NFS: Not further specified
P: Placebo
P.H.: Public Health
PG: Proguanil
preg: Pregnancy
RCT: Randomized controlled trial
w/: With
w/o: Without
T: Tablets
wk: Week

