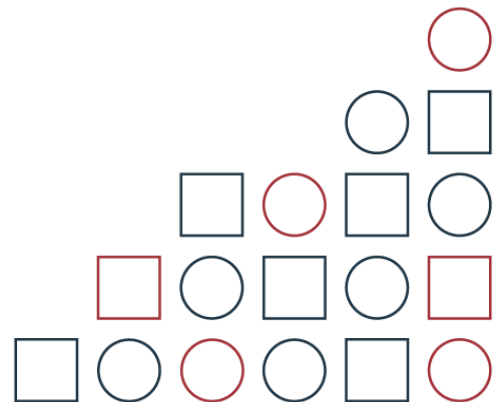


# Frequently Asked Questions

**Weekly Iron Folic Acid Supplementation (WIFAS) for Adolescents**

**August 2022**



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## Section 1: Intervention overview

### 1. What are WIFAS?

Weekly Iron and Folic Acid Supplements, or WIFAS, are oral supplements to prevent and reduce anaemia, which consist of 60 mg of elemental iron and 0.4 mg of folic acid, or, where available, they may consist of the World Health Organization (WHO) recommended dose of 2.8 mg of folic acid<sup>1</sup>. They are recommended by the WHO as a preventative public health intervention for adolescent girls and menstruating women living in areas where the prevalence of anaemia in adolescent girls and women of reproductive age (WRA;15-49 years of age) is 20% or greater. The current guidelines for intermittent iron and folic acid supplementation state that the supplement should be taken at minimum once weekly, usually on a predetermined day and time for a period of three months, followed by a three month period with no supplementation for a total of six months per year. After this, supplementation should restart<sup>1</sup>. Alternatively, if feasible, supplements can be given throughout the school calendar year and a break from supplements aligned with school vacations. Some countries may also provide supplements every week for up to 52 weeks. For adolescents, it is recommended for girls from 10-19 years of age.

### 2. Why is the supplement taken weekly?

WIFAS has been recommended as a public health approach for: 1) efficiency of absorption; and 2) increased adherence. Intestinal cells turnover every five to six days, and thus have limited absorptive potential. However, once weekly supplementation would expose only new cells with iron, which could increase absorption<sup>2,3</sup>. It is also thought that intermittent supplementation can reduce oxidative stress, minimize absorptive competition between iron and other minerals, and reduce some of the unpleasant reported side effects associated with daily supplementation<sup>4,5</sup>. Additionally, WIFAS intermittent supplementation programs have been shown to increase adherence and acceptability among participants, making it a cost efficient option for anaemia reduction, compared with daily supplementation<sup>6,7</sup>.

### 3. Why are iron and folate important micronutrients for adolescent girls?

Adolescence is the period with the second highest rate of growth in a person's life, second only to infancy<sup>8</sup>. Since this period of growth is longer than that of infancy, adolescents have greater nutritional needs during puberty than any other period of life<sup>8</sup>. Adolescents have increased needs of certain nutrients to support their rapid growth. One such nutrient is iron, which is important for adolescents' expanding blood volume, development of lean body mass, as well as counteracting menstrual blood loss in females<sup>8</sup>. Additionally, folate is an important nutrient for red blood cell formation and growth, DNA production and repair, and normal cell functioning which contribute to adolescents' growth and development<sup>9</sup>. The recommended daily dietary intake of folate for adolescents is between 0.3 mg (9-13 years) and 0.4 mg (14-19 years)<sup>10</sup>. For adolescents who become pregnant, these needs are much greater at 0.6 mg per day<sup>10</sup>.

Due to their increased need for iron, and often low dietary intake of iron, many adolescents in low- and middle-income countries (LMIC) are at an increased risk of having iron deficiency anaemia. In fact, iron deficiency anaemia is currently the leading cause of years lived with disability in

adolescent girls 10-19 and boys 10-14, as measured by DALYs (Disability Adjusted Life Years)<sup>11</sup>. This is further exacerbated in females, as the beginning of menstruation increases their iron needs and additionally girls have lower iron stores than boys<sup>8</sup>. Due to this, and social risks for lower dietary iron intake, adolescent girls are at an increased risk of anaemia and its negative consequences, which can include reduced physical work capacity, fatigue, and reduced cognitive ability, which can directly affect their school performance. For adolescents who do become pregnant there are also increased risks for negative birth outcomes for the mother and infant.

Once weekly supplementation with IFA is a cost-effective method for reducing iron deficiency anaemia where it is of public health concern and delivery platforms to reach girls are available.

The rapid period of growth during adolescence demands adequate intake of folate. In many LMIC's, the estimated prevalence of folate deficiency in women aged 12-49 years is greater than 20%<sup>9</sup>. Folate deficiency can also cause other forms of anaemia; however, the global burden of anaemia caused by folate deficiency is very low<sup>12</sup>. Folic acid is very important during pre-conception, and early pregnancy as poor maternal folate status can be a risk for neural tube defects (NTDs)<sup>13,14</sup>.

#### 4. What is the recent evidence that folic acid in WIFAS can prevent NTDs?

NTDs are severe birth defects that can occur within the first 28 days of pregnancy<sup>15</sup>. In 2015, the global number of NTD-affected pregnancies was 260,100, which resulted in 117,900 under-five deaths<sup>16</sup>. Spina bifida and anencephaly are the most common and are associated with neonatal mortality, morbidity, and long-term disability<sup>16</sup>. NTDs can be prevented by improving folate status before conception and during very early pregnancy, by supplementing with folic acid, through food fortification with folic acid and by consuming folate-rich foods<sup>13,17</sup>. However, half of all pregnancies worldwide are unplanned, and the neural tube closes within six weeks of pregnancy, which is before many women know they are pregnant<sup>18</sup>. Therefore, women may not choose to consume daily prenatal supplements with folic acid, and many others may not have access. After the neural tube has closed, the window of opportunity for preventing NTDs by folic acid intervention may be missed.

Until recently, data was not available on the efficacy of WIFAS with 60 mg iron + 2.8 mg folic acid to increase folate status and protect pregnancies from NTDs. A recent Nutrition International supported randomized control trial conducted in Malaysia in 2019 aimed to fill this evidence gap<sup>19</sup>. The study investigated the efficacy of weekly iron (60 mg) with two doses of folic acid and placebo (2.8 mg, 0.4 mg, and 0 mg folic acid) on red blood cell (RBC) folate concentrations and plasma folate in non-pregnant women aged 18-45 years old<sup>19</sup>. RBC folate was used as it is an established biomarker for NTD risk, and the WHO recommends RBC folate levels above >906 nmol/L<sup>1</sup> to prevent NTDs<sup>15</sup>. The study found that WIFAS using the WHO-recommended dose of 2.8 mg of

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<sup>1</sup> The randomized control trial in Malaysia used an adjusted RBC folate concentration population cut-off value recommended by the U.S. Centers for Disease Control and Prevention of >748nmol/L. After adjustment, this value was equivalent to the WHO recommended population cut-off of >906nmol/L.

folic acid increases RBC folate concentrations to levels that can reduce the risk of NTD-affected pregnancies among women and adolescents.

## 5. Why are WIFAS programs often only for girls 10-19 years old?

Adolescents are defined by WHO as people between 10-19 years of age<sup>20</sup>. Adolescent girls have been the main focus of WIFAS interventions in many countries, moreover, the WHO guidelines are for adolescent girls and women. It has been found that accessing adolescent girls through the health system can be unfeasible, as they often are among the least likely to access health facilities for preventative health services. Thus, the best way to reach them is through already existing platforms and partnerships, often beyond health<sup>21</sup>. In contexts where school attendance is high, schools are the most cost-effective delivery platform, with Ministry of Education as a key partner. Out-of-school girls are among the most vulnerable and different strategies are needed to reach them.

While adolescent nutrition programs typically target girls 10-19 years old, WIFAS programs have been shown to be effective for girls 10-19 years of age, as well as women 20-49 years of age<sup>21,22</sup>. In fact, WIFAS could have benefits for reducing anaemia and preventing NTD affected pregnancies for adolescent girls and adult women in populations where the prevalence of anaemia in menstruating females (15-49 years of age) is greater than 20%. Thus, supplements could be taken from the time of menarche through to menopause<sup>1</sup>. However, in practice it is not necessary or practical to confirm menarche, as the intervention prevents anaemia and currently programs are mainly reaching adolescents.

Therefore, it should be noted that if there are female students in schools older than 19 years, they should be encouraged to continue to be part of the program and take the supplements as well. Additionally, the WHO guidelines recommend women of reproductive age older than 19 years of age would also benefit from WIFAS. However, different delivery platforms and partnerships would be required for programs for delivering WIFAS to women of reproductive age (20-49 years).

## 6. Why are boys not included in most WIFAS programs?

Adolescent males do not receive WIFAS supplementation in many contexts because their physiological iron needs are not as high as those of adolescent females<sup>23</sup>. For example, males do not need to account for menstrual losses in their iron needs. They also generally have larger iron stores in their bodies than females. However, adolescent boys may receive WIFAS in contexts where their anaemia rates are high. For instance, currently, Nutrition International's program in India does include supplementation for boys. The anaemia prevalence in women of reproductive age is often higher than that of adolescent girls, as risk for anaemia increases. In some contexts, anaemia is higher in adolescent males than in adult men, suggesting that the future risks of anaemia may decrease for boys.

## 7. What are alternatives to WIFAS for reducing anaemia in adolescent girls?

Interventions that have been implemented in order to improve adolescent nutrition have included efforts such as promotion of healthy diets and eating practices, fortification of staple foods, and promotion of physical activity, among others. However, while intervention efforts have existed, implementation has been limited, and there is very little evidence of their effectiveness as a public health approach.

WIFAS is one of the limited examples of nutrition interventions with proven effectiveness to impact adolescent girls' nutritional status, as evidenced through previous anaemia reduction programs in the Asia region. A 2011 Cochrane review, which informed the WHO guidance, was updated in 2019 and found that intermittent iron supplementation in girls and women (6-49 years), alone or with other vitamins and minerals, reduced the risk of anaemia by 35%<sup>22</sup>.

IFA supplementation and iron supplementation have both been found to be effective at reducing the prevalence of anaemia and increasing haemoglobin concentrations<sup>24</sup>. Multiple micronutrient supplementation has also been found to significantly improve haemoglobin concentrations in adolescents<sup>24</sup>. However, it should be noted that daily iron supplementation programs have not been effective as a public health approach for adolescent girls and women in practice due to low coverage rates, insufficient tablet distribution, and low adherence due to reported unwanted side effects (e.g. constipation, dark stools, and metallic taste)<sup>25</sup>. It has been suggested that weekly intermittent regimes may be more acceptable to participants and increase adherence<sup>1</sup>.

While food fortification interventions, such as those for industrially processed flour, maize or corn meal, when appropriately implemented, are an efficient, inexpensive strategy for supplying vitamins and minerals to the diets of large segments of the population, this is a much longer-term strategy. An intervention like WIFAS supports anaemia reduction efforts in the short term and by targeting a vulnerable group, such as adolescent girls, which can be concurrent to broader, often national initiatives like food fortification.

Promotion of dietary diversity and interventions for dietary modification can increase dietary iron intake by promoting increased consumption of iron-rich foods. They may also increase the absorption of iron through foods through processing techniques that reduce inhibitors (such as phytates) or increase enhancers (such as ascorbic acid (vitamin C)) for non-heme iron absorption. However, these interventions do not have evidence as a scalable public health approach, as food insecurity, including limited access to iron-rich, and especially animal source foods, is often a barrier to increasing dietary consumption of iron. Food based approaches can be complementary to supplementation<sup>20</sup>.

## Section 2: WIFAS and Anaemia

### 8. Is WIFAS for treating anaemia? What is the dose for treating anaemia?

No, WIFAS programs are not for treating anaemia, rather WIFAS is a public health intervention for anaemia prevention in adolescents and non-pregnant WRA<sup>1</sup>. To treat severe anaemia in

adolescents (defined as hemoglobin levels <7 g/dL or hematocrit below 20%), daily supplementation with 120 mg iron and 0.4 mg folic acid should occur for a period of 3 months<sup>26</sup>. Following this, if haemoglobin concentrations return to normal, a preventative regimen, such as WIFAS, should commence.

## 9. What are the signs and symptoms of anaemia?

Anaemia can range from mild to severe with a range of signs and symptoms. Some common signs and symptoms of anaemia include fatigue, weakness, difficulty concentrating, brittle or spooned nails, pale skin, cracks at the sides of the mouth, coldness in the feet and hands, pica, shortness of breath, and, in severe cases, irregular heartbeat<sup>27</sup>.

## 10. Should we screen for anaemia before starting WIFAS?

Because WIFAS is not a targeted program and it is preventative, screening is not done as it is not cost-effective where anaemia in women of reproductive age is >20%. Therefore, girls are not tested for anaemia through this program prior to receiving weekly supplements. However, should a girl present with signs and symptoms of anaemia, such as those mentioned above, she should be referred to a local health center for follow-up, to be assessed and given treatment as appropriate.

## 11. Do WIFAS formulated with 2.8 mg folic acid result in greater benefits for anaemia reduction?

WIFAS formulated with 0.4 mg, 2.8 mg folic acid or iron only show equal benefits on anaemia reduction. The recently conducted efficacy trial in Malaysia found that while folate deficiency anaemia was low amongst study participants, the greater amount of 2.8 mg folic acid in WIFAS does not result in additional benefits for reducing anaemia, improving hemoglobin concentrations, or improving iron status<sup>28</sup>. However, where WIFAS are to be used as an approach for NTD prevention, the WHO formulation of WIFAS with 2.8 mg folic acid should be used<sup>28</sup>. This is because it is seven times more effective in increasing RBC folate concentrations to levels above WHO recommendations for NTD prevention than WIFAS with 0.4 mg of folic acid<sup>19</sup>.

## Section 3: Benefits of WIFAS

## 12. What are the benefits of WIFAS to prevent anaemia?

WIFAS prevents and reduces the risk of anaemia in the population and improves iron status<sup>22</sup>. There is lost potential from anaemia in adolescent girls and women. This can include decreased school performance, loss of productivity, and in the event of adolescent pregnancy, anaemia has negative health outcomes for the adolescent mother and her infant.



WIFAS have been found to reduce the risk of anaemia and improve concentrations of haemoglobin and ferritin with fewer side effects than daily supplementation<sup>22</sup>. This improvement in haemoglobin and possible reduction in anaemia could lead to improvements in brain function and subsequent school performance<sup>21,29</sup>. Girls could also find that they feel more energized and have an improved capacity for physical activity and exercise<sup>30</sup>.

Adolescent girls who took WIFAS regularly qualitatively described a positive impact on “enhanced skin glow and improved appearance”, which could result from an improvement in haemoglobin concentrations<sup>21</sup>; however, there is no available evidence to support this or other claims related to beauty. WIFAS can be positioned as a product for girls to feel strong and beautiful, but it is important not to make false claims about WIFAS improving beauty.

### 13. What are the benefits of WIFAS to prevent NTDs?

WIFAS using the WHO recommended dose of 2.8 mg of folic acid can reduce the risk of NTDs. The efficacy trial conducted in Malaysia found that non-pregnant women who received WIFAS formulated with 2.8 mg folic acid had a 271 nmol/L greater mean RBC folate than those receiving the 0.4 mg dose<sup>19</sup>. Additionally, WIFAS formulated with 2.8 mg folic acid were seven times more effective in increasing RBC folate to levels associated with reduced risk of NTD-affected pregnancy than the 0.4 mg dose<sup>19</sup>. The study concluded that WIFAS formulated with 2.8 mg folic acid can improve RBC and plasma folate concentrations to levels that protect against NTDs should a woman become pregnant. NTD prevention through WIFAS is important for adolescent girls as each year approximately 10 million unplanned pregnancies occur among girls aged 15-19 years in low and middle-income countries<sup>31</sup>.

However, the effectiveness and cost-effectiveness of WIFAS as a strategy to prevent NTDs depends on reaching adolescent girls and women in the preconception period and in the first month of pregnancy, before the neural tube closes. In-school WIFAS programs are at varying stages of implementation, globally. India may be one of the only countries with a nationwide program implemented across states with both school and community-based platforms. Many other countries are in the early implementation or scale up phases, with most reach through school-based delivery. Many of these programs may not be reaching many of the adolescent girls who may become pregnant; however, adolescents in school who become pregnant may benefit. Consideration should be given to the target population, folate deficiency, rate of NTD-affected pregnancies and access to other folic acid supplementation programs (e.g., food fortification).

### 14. How do WIFAS affect school performance?

A 2010 review of 14 trials examined the effects of oral iron supplementation on cognitive performance in older children and adults (children aged 6+, adolescents, and women)<sup>32</sup>. The trials included providing daily iron supplementation ranging from 17mg/day to 260mg/day. Two trials provided iron supplementation at a dose of 2mg/kg/day, and one provided a dose of 4mg/kg/day. In addition to daily iron supplementation, one trial also included a group that

received a weekly iron dose of 60mg. This review found that iron supplementation, independent of baseline iron status improved attention and concentration<sup>32</sup>. In participants with anaemia, supplementation significantly improved their IQ score, but this effect was not seen in non-anaemic participants<sup>32</sup>. Additionally, a 2013 review of oral iron supplementation in primary school-aged children found that supplementation improved global cognitive scores, IQ scores in anaemic children, and measures of concentration and attention<sup>33</sup>. A 2022 systematic review including 50 studies also found that iron interventions during adolescence may improve school performance, attention, and concentration in some contexts<sup>34</sup>.

There is no direct evidence assessing the effectiveness of WIFAS in adolescents 10-19 years of age and the benefits on school performance or dimensions of learning.

## 15. What happens if a girl does not take WIFAS?

Many girls with mild anaemia may be unaware that they have anaemia. Girls do not need to be or appear sick in order to take WIFAS, as it is not a treatment for anaemia. All girls without other medical contraindications in contexts where anaemia is of public health concern (>20% in females 15-49 years) are recommended to take WIFAS as a preventative measure against anaemia and its negative consequences. While taking WIFAS is of course strongly recommended, remember that it is completely voluntary. However, if a girl chooses not to take the supplement she may be at higher risk of anaemia and its consequences, such as fatigue, reduced physical work capacity, and reduced cognitive function.

Adolescent girls and women who have unplanned pregnancies may not supplement with the daily IFA during preconception and early pregnancy, especially not before a missed period. WIFAS containing 2.8 folic acid can reduce the risk of an NTD-affected pregnancy<sup>19</sup>, by improving folate status preconceptionally. If adolescent girls do not take WIFAS containing 2.8 mg of folic acid, they may have a higher risk of having an NTD-affected pregnancy if they become pregnant. WIFAS programs using the WHO-recommended dose of 2.8 mg of folic acid are especially important for countries where there is no food fortification with folic acid, or the consumption of fortified foods is low among girls and women.

## 16. To maximize benefit, how can we increase adherence and increase consumption of WIFAS?

In order to ensure adherence and consumption, the girls must receive the supplements. For example, in a school-based program this means they need to be at school on WIFAS day, supplies need to be available at schools, and teachers need to feel motivated and confident to give out supplements to their students.

There is a clear link between school attendance and program adherence. Thus, one of the best long-term strategies to ensuring that supplements are consumed will be to break down barriers that students face in attending school. A fixed day approach can also be part of ensuring supplements are given out on the day when the most girls will be at school<sup>35</sup>. Follow-up with

classroom, peer-based or alternative delivery strategies can be used for when a student is absent on the supplementation day.

Being prepared to support girls in the early weeks of supplementation, such as at the beginning of the school semester is critical, as this is when side effects are most likely to occur. While they will likely lessen over time, support in preventing or managing side effects can influence a girl's willingness to keep taking a supplement<sup>36</sup>. Availability of clean water and timing the supplement consumption to be closest to a meal or snack can reduce side effects (see Question 21).

Strategies to increase adherence for girls who are at school can include individual cards held by the participants; the cards engage girls in the intervention and serve as a reminder of the benefits of using WIFAS regularly and to consume the supplement on a specific day<sup>21</sup>.

If the supplement with the 60 mg iron + 2.8 mg folic acid is to be used for anaemia reduction and NTD prevention, adolescents and parents may have concerns about the supplement and mistakenly feel it is some kind of contraceptive, or not relevant for an adolescent not planning to become pregnant. Parents and adolescents can be reminded of its safety and benefits for anaemia reduction and being the MoH and WHO recommended product.

## 17. What are best practices for monitoring coverage and adherence?

Proper monitoring can help program managers track the coverage of programs, identify and reduce dropouts, and develop strategies to increase adherence<sup>21</sup>.

Monitoring registers at the class or school level, where a teacher enters information each week, have been found to be practical, simple, and acceptable by teachers<sup>21</sup>. Such registers can be modeled after existing attendance forms and can record information on side effects and discontinuation of WIFAS, which is useful for following up on low adherence cases and arranging subsequent counselling sessions. As WIFAS are a health intervention often delivered at schools, harmonization and collaboration between education and health partners are essential for developing forms and data that work for both sectors. Digital platforms may be an option in some settings where digital health and/or education strategies are in place. Ideally, WIFAS can be integrated and included into HMIS.

## Section 4: Safety considerations

### 18. Is it safe to consume WIFAS?

Yes, WIFAS are safe to take once a week. The interim supplement being used in many countries (60 mg iron and 0.4 mg folic acid) and the WHO-recommended WIFAS formulation (60 mg iron and 2.8 mg folic acid) is well below the weekly upper limit for both folic acid (7 mg/week) and iron (280-315 mg/week) set by the Institutes of Medicine<sup>23</sup>. Folic acid is also a water-soluble B-vitamin, which means it dissolves in water when consumed and the body does not store it in excess<sup>37</sup>.

Thus, if only *one supplement* is taken per week as recommended, it will be safe and will not be possible to overdose.

## 19. Is it safe to consume WIFAS over long time periods?

Yes, it is safe to consume WIFAS over long and/or multiple time periods as the current weekly formulation is well below the weekly upper limits set by the Institutes of Medicine<sup>10,23</sup>. A recent study showed sustained effectiveness of WIFAS over six years, which also indicates that it is safe to take for multiple years<sup>38</sup>. Additionally, as mentioned in Question 5, the current WHO guideline recommends WIFAS for all menstruating adolescent girls and women<sup>1</sup>. Females have higher iron needs until they reach menopause, thus consuming WIFAS from the time of menarche through to menopause will help them to meet their physiological iron needs while also reducing the risk of anaemia (33% of women of reproductive age are anaemic globally)<sup>39</sup>. Any side effects associated with WIFAS usually occur early on in the supplementation regime and normally decrease over time<sup>21</sup>.

## 20. Is it safe to use WIFAS formulated with 2.8 mg folic acid in countries with folic acid food fortification?

WIFAS containing 2.8 mg acid are safe in countries with folic acid food fortification. The tolerable upper intake level for habitual daily consumption set by the Institute of Medicine is 1 mg/day<sup>10</sup> and WIFAS is provided once weekly. The amount of folic acid consumed from fortified foods is estimated at less than 0.6 mg/day and the tolerable upper intake level for folic acid does not include intake from food sources<sup>40-43</sup>. Therefore, folic acid intake from fortified foods and weekly supplementation with 2.8 mg would still be below the tolerable upper intake for folic acid. Additionally, as mentioned in Question 18, folic acid is a water-soluble B-vitamin that is not stored in excess in the body<sup>37</sup>. There is no conclusive evidence to support adverse health outcomes of high folic acid intake<sup>44-49</sup>. Studies have tested similar or higher doses of weekly folic acid without reports of adverse side effects<sup>50-54</sup>. A combination of approaches can be used to prevent NTDs and improve population folate status.

## 21. Are there any girls who should be excluded from taking WIFAS?

It should be noted that girls who are diagnosed as having anaemia are not recommended to take WIFAS, where clinical procedures are in place. Instead, anaemic girls should be treated using her country's clinical guidelines. WHO recommends that if anaemia is diagnosed, the girl should be treated with daily iron (120 mg of elemental iron) and folic acid (0.4 mg) supplementation until her haemoglobin concentrations rise to normal levels. Following this, she can take WIFAS to prevent the anaemia from returning<sup>1</sup>.

Additionally, pregnant adolescent girls should not consume WIFAS. They should be supported to receive Antenatal Care (ANC) from trained providers, and they should receive daily iron folic acid supplements as their iron needs are much higher than that of non-pregnant adolescent girls. WHO

ANC guidelines recommend 60 mg iron with 0.4 mg folic daily during pregnancy and three months post-partum<sup>55,56</sup>. Additionally, recent evidence now supports multiple micronutrient supplementation (MMS) containing iron and folic acid to be effective in improving birth outcomes and preventing maternal anaemia<sup>57-60</sup>. The WHO ANC guidelines now also recommend context-specific MMS containing 30 mg-60 mg iron and 0.4 mg folic acid during pregnancy in countries with a high prevalence of micronutrient deficiencies<sup>60</sup>.

WHO recommends that WIFAS are formulated to supply a weekly dose of 60 mg iron and 2.8 mg folic acid, but this formulation is not readily available<sup>1</sup>. The WIFAS will not harm a pregnant women or pregnant adolescent; however, her iron needs are greater and folic acid is proven effective for prevention of neural tube defects (NTD) with the daily dose. Should an adolescent girl or woman determine she is pregnant while on WIFAS, she should discontinue her use of the weekly supplement when she is able to begin consuming the WHO recommended daily supplement.

In the case of illness, including malaria or other acute infections, healthcare providers may recommend suspending WIFAS until the course of treatment is complete (see Questions 22 and 23).

## 22. Is it safe for teachers to administer WIFAS?

Yes, it is safe for teachers to administer WIFAS. As the best method for implementing WIFAS in many contexts is through utilizing existing school structures it is also helpful to have the support of the teachers. In prior experience implementing WIFAS in the Asia region, teachers were found to be effective distributors and monitors of the WIFAS supplements<sup>21</sup>. Additionally, they are trusted and considered credible by the girls, which can also help to boost acceptance and success of the program<sup>21</sup>.

## 23. Is it safe to supplement throughout the school calendar year?

Yes. There are no safety concerns associated with giving WIFAS throughout the school calendar year. The most important aspect is that the girls take the WIFAS for at least six months of the year as this is typically the amount of time iron therapy is needed to have the desired positive effect on their haemoglobin levels, as well as to increase the body's iron stores<sup>61</sup>.

In considering aiming for at least a minimum of six months of supplementation in a year, the WHO guidelines recommend a three months on followed by three months off regimen, after which supplementation should resume with another three months, and so on. The guideline also suggests aligning with the school calendar year, as an option. However, this is only a suggestion, and there is no concern with aligning WIFAS supplementation in a way that is more convenient for those delivering the programs, such as aligning with ongoing program delivery through other platforms. Some countries also offer supplements every week of the year for 52 weeks.

## 24. What are the impacts of the various WHO-recommended dosing schedules on NTD prevention?

The benefits of WIFAS on NTD prevention is reduced if WIFAS is paused for four 4 weeks or longer. The randomized control trial conducted in Malaysia among non-pregnant women (18-45 years old) provided 16 weeks of WIFAS using two doses of folic acid compared with a placebo<sup>19</sup>. After 16 weeks, supplementation was stopped for four weeks to simulate school holiday periods<sup>19</sup>. At 16 weeks, 68% of participants receiving 2.8 mg folic acid had a mean RBC folate above recommended levels for NTD prevention compared with only 8% in the 0.4 mg group and 4% in the iron only group. The study found that after four weeks with no supplementation, at 20 weeks mean RBC folate concentrations decreased in women receiving both doses of folic acid (0.4 mg and 2.8 mg). More than 50% of women receiving 2.8 mg folic acid still had mean RBC folate concentrations above population levels associated with NTD prevention compared to 11% in the 0.4 mg group.

Folate status declines with a break from supplementation; however, these findings suggest that WIFAS formulated with 2.8 mg folic acid are more likely to protect against NTDs (RR 4.2, 95%CI 2.4 to 7.3) compared to WIFAS with 0.4 mg folic acid<sup>19</sup>.

## 25. Are there side effects associated with WIFAS?

There are some side effects associated with taking WIFAS related to iron. These can include black stools, nausea, constipation, abdominal cramping, and vomiting. However, these side effects are typically reported only in the first few weeks of use and normally decrease over time<sup>21</sup>. It is very important to inform everyone participating in the program of the possible side effects and note that they are normally mild and transient. Folic acid in WIFAS has not been associated with side effects. There are no differences in side effects between WIFAS formulated with 2.8 mg folic acid and 0.4 mg folic acid.

## 26. How can the side effects be managed?

Side effects have been commonly associated with taking the supplement on an empty stomach. Thus, to reduce the chance of side effects, it is best to take the supplement within two hours of consuming a meal<sup>21</sup>. Each program can assess what might be optimal timing, for example, in some countries girls eat before coming to school. However, if food is unavailable, or if schools do not provide any food, it is still safe to consume the supplement without a meal. WIFAS will still be effective as the iron and folic acid can be absorbed without the presence of food.

If this is the case, it is recommended that the girls take their WIFAS with water. Schools can recommend girls to bring a bottle/canteen of water with them from home on assigned WIFAS days. There may also be seasonal considerations, such as those for areas that observe Ramadan. During this season, WIFAS supplements could still be sent home with the girls so that they can take them with water and food once they had breakfast.



## 27. Can WIFAS be administered in areas with haemoglobinopathies?

In areas where haemoglobinopathies (e.g. sickle cell disease and thalassemy) are endemic, a screening program is recommended before commencing an iron supplementation program. This is because iron deficiency may not be the cause of anaemia, and supplementation will therefore not be an effective anaemia reduction strategy<sup>62</sup>.

## 28. Can WIFAS be administered in areas with malaria?

It is safe to take weekly iron folic acid supplementation in malaria endemic areas. In these areas, the provision of weekly iron and folic acid supplements should be implemented in conjunction with adequate measures to prevent, diagnose and treat malaria<sup>1</sup>.

Recent evidence suggests that iron and folic acid supplements consumed once, twice or three times a week on non-consecutive days by adolescents and women of reproductive age are an effective, safe, and more acceptable alternative to daily iron supplements, including in settings where malaria is endemic<sup>63</sup>.

As a precaution, in a case where a girl is infected by malaria and is taking treatment for it, a healthcare provider may recommend that she not take WIFAS while she is being treated. She may resume taking WIFAS once the course of malaria treatment is complete, upon healthcare provider guidance.

## Section 5: WIFAS and reproductive health

### 29. Are WIFAS a contraceptive?

No, this nutritional supplement is not a contraceptive. The formulation contains iron and folic acid which are not contraceptive agents. A girl can still become pregnant while taking WIFAS supplements as it is neither a reproductive tool nor a family planning method.

Pregnancy in adolescence is associated with higher risks for negative health outcomes for both the adolescent mother and the baby. For example, adolescent mothers are at higher risk of eclampsia and systemic infections than mothers aged 20-24 years, while newborns born to young mothers are at increased risk of low birthweight, preterm delivery, and other severe neonatal conditions<sup>64</sup>. In programs, it must be emphasized that if a girl has sex without effective contraception, she may still become pregnant, as WIFAS is not a contraceptive.

In many cases there is stigma with girls accessing contraceptives. It may be important for parents to know that WIFAS are not contraceptives, in order to support their adolescent girls' consumption and participation in the adolescent nutrition program. Routine consumption of WIFAS with 2.8 mg folic acid can protect an unplanned pregnancy from being affected by NTDs;

however, a broader goal of the adolescent nutrition programs is to prevent unintended pregnancies. Broader adolescent nutrition strategies can consider that delaying pregnancy beyond adolescence and reducing number of pregnancies before the age of 18 can have nutritional and health benefits for adolescents and accessing contraceptives or information about sexual and reproductive health may be part of this.

### 30. Do WIFAS help regulate menstruation?

Girls who are underweight and gain weight may experience increased regularity in menstruation, or return of menstruation, if periods were absent. There is currently no evidence that links iron supplementation with improving or influencing menstruation. WIFAS contain iron and folic acid (vitamins and minerals), which do not provide calories and are therefore unable to improve upon the chronic negative energy balance that causes menstrual irregularity or nutritional amenorrhea<sup>65</sup>.

As these are not targeted programs and WIFAS is a preventative intervention, it is not necessary to confirm a girl's menstrual status. In many settings it may not be appropriate for teachers to ask a girl about menarche as part of the Adolescent Nutrition programs, especially if a teacher is male.

### 31. Will using WIFAS formulated with 2.8 mg folic acid impact the recommendations for daily IFA supplementation during pregnancy?

Daily supplementation with 60 mg iron and 0.4 mg folic acid or MMS containing 30-60 mg iron and 0.4 mg folic acid remains the best practice to prevent NTDs for women who are planning pregnancy<sup>55,60</sup>. In cases where women are not planning on becoming pregnant or do not take the daily IFA supplement, WIFAS containing the WHO-recommended dose of 2.8 mg folic acid is a more effective public health approach for reducing the risk of NTDs than 0.4 mg folic acid once per week<sup>19</sup>.

Women and adolescent girls taking WIFAS containing 2.8 mg folic acid should switch to the daily recommended IFA supplementation or MMS that includes 0.4 mg daily folic acid once they become aware they are pregnant.

## Section 6: WHO-recommended formulation

### 32. What should a country do when the WHO formulation is not available?

Currently, the formulation of WIFAS outlined in the WHO guideline (60 mg elemental iron and 2.8 mg folic acid) is not included in the 22<sup>nd</sup> WHO Model List of Essential Medicines,<sup>66</sup> though the new formulation is available in the UNICEF catalogue<sup>67</sup>. As this model WHO EML list is what many countries base their national essential medicines lists on, this formulation is unlikely to be on national essential medicines lists, which guide a country's procurement and supply of medicines.



In addition, a market scoping found that there are limited manufacturers globally currently making the WHO recommended supplement (60 mg iron and 2.8 mg folic acid), while a couple of others have expressed interest in future production. While efforts progress to make the supplement more globally and commercially available, programs are recommended in the interim to use the same supplement as that used in many contexts for daily IFA supplementation in pregnant women (60 mg iron and 0.4 mg folic acid). The prenatal dose with 60mg iron and 0.4 mg folic acid is safe to use for adolescents once weekly as it does not exceed the weekly upper limits for both folic acid (seven mg/week) or iron (280-315 mg/week) set by the Institutes of Medicine<sup>10,23</sup>. This supplement is being used because it has the same weekly iron dose (60 mg) that is recommended for anaemia reduction<sup>1</sup>. Although, this dose of folic acid (0.4 mg) is lower than that recommended by WHO for NTD prevention and will not have equal benefits on NTD prevention.

### 33. How can I differentiate the IFA for pregnant women from the IFA for adolescent girls?

The WHO-recommended weekly dose for adolescent girls (60 mg iron and 2.8 mg folic acid) is not the same as the daily dose for pregnant women (60 mg iron and 0.4 mg folic acid)<sup>1,55</sup>. However, as market scoping to date has found limited manufacturers that currently produce the WHO formulation of WIFAS, it is recommended that the daily dose for pregnant women be used for WIFAS programs until the commercial availability and affordability of the 60 mg iron and 2.8 mg folic acid formulation is increased. Once the WIFAS formulation is readily available and accessible, it will have a different package and shape than the prenatal formulation for pregnant women, which will make it easy and clear to differentiate between the two supplements. It is important to note that some countries also have multiple micronutrient supplements or 30 mg IFA formulations available for pregnant women<sup>67</sup>. As of 2019, The UNICEF supply catalogue now includes the WHO WIFAS formulation (60 mg iron and 2.8 mg folic acid)<sup>68</sup>. This product is listed as “anti-anaemic” and contains pink tablets.

### 34. Will using the same IFA supplements for pregnant women in WIFAS programs result in stockouts?

As in many settings both adolescent programs and maternal health programs are currently using the same supplement (60mg iron + 0.4mg folic acid), there is valid concern that either or both programs will face stockouts due to drainage of one’s supply for the other when the two programs use the same supplement.

In order to ensure this does not happen, concerted and collaborative effort will be required from both programs. Mitigating strategies should include joint forecasting, and procurement and supply management plans, considering the needs and requirements of both populations. Including these details in one clear plan will facilitate adequate supply is available for both programs, and that pregnant women and adolescent girls will benefit from anaemia reduction efforts. The forecasting exercises will likely require collaboration of education and other sectors, where schools and/or social welfare programs are involved in the delivery to adolescents.

However, if the WHO-recommended WIFAS dose (60 mg iron and 2.8 mg folic acid) is added to the WHO Model List of Essential Medicines and countries choose to use this supplement, this may lead to more availability and affordability of the supplement for WIFAS programs. In addition, using the WHO-recommended dose will ensure WIFAS programs are using a different supplement from other maternal health programs, reducing the likelihood of stockouts.

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