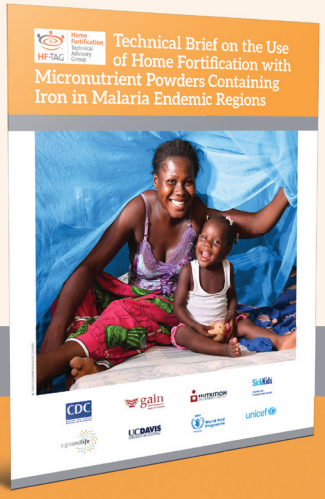
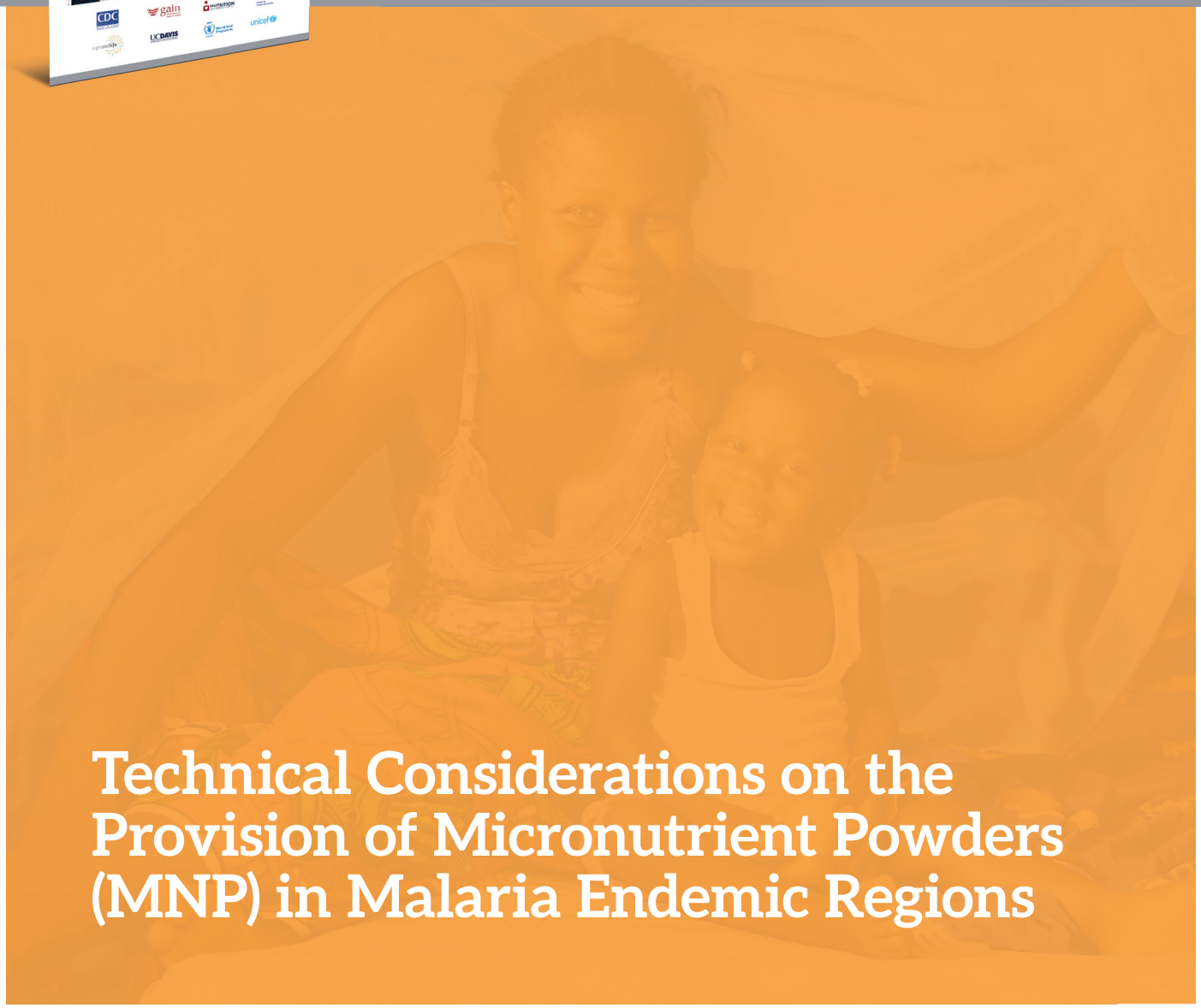


HF-TAG Home Fortification Technical Advisory Group

Frequently Asked Questions



Technical Considerations on the Provision of Micronutrient Powders (MNP) in Malaria Endemic Regions

CDC Centers for Disease Control and Prevention

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Preamble

This document provides additional technical information that can be applied to the most recent "*WHO Guideline: Use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children aged 6–23 months and children aged 2–12 years*"[1], specifically in countries implementing programs with MNP in malaria endemic regions. It is an accompanying resource to the "*Technical Brief on the use of Home Fortification with Micronutrient Powders Containing Iron in Malaria Endemic Regions*".[2] The goal of this document is to provide additional information related to some common questions that may arise when planning and implementing MNP interventions in countries or regions that include malaria-endemic areas.

Micronutrient powders can be used to improve the quality of complementary foods for infants and young children and the quality of the diet for other vulnerable populations; thus, they are an important component of nutrition programs. Most public health programs distributing MNP use a formulation that contains at a minimum iron, vitamin A, and zinc, and many MNP are formulated with 15 vitamins and minerals.[3]

The WHO guideline clearly recommends that children 6 months to 12 years of age in malaria-endemic areas are not to be excluded from receiving iron-containing MNP, as these children are also at risk of significant morbidity, including malnutrition. However, because of the association between anemia and malaria, and due to any potential risks, WHO also recommends that any home or point-of-use fortification with iron should be implemented in conjunction with measures to prevent, diagnose, and treat malaria. This resource, in combination with the broader Technical Brief, is intended to assist with some of the technical and programmatic considerations that need to be taken into account in order to adhere to these recommendations.

Providing iron safely to children in malaria endemic regions is a key area of focus within the WHO guideline; however, the guideline does not make any recommendations either for or against the inclusion of folic acid in MNP. In many cases, MNP formulations include folic acid, which raises concerns due to the potential antagonistic relationship between folic acid and antifolate drugs, including antimalarials. This document also provides technical information on this topic.

Information included in this resource is primarily intended to be used by program managers who are responsible for planning and implementing programs that include MNP and to address some existing concerns and questions that may arise. It is based on literature reviews, country experiences, and the opinion of technical experts working in the nutrition and malaria fields. As a "living document", it will be updated periodically as new information and literature become available.

1 WHO Guideline: Use of multiple micronutrient powders for point-of-use fortification of foods consumed by infants and young children aged 6–23 months and children aged 2–12 years. November 2016

2 Home Fortification Technical Advisory Group. Technical Brief on the Use of Home Fortification with Micronutrient Powders Containing Iron in Malaria Endemic Regions. Home Fortification Technical Advisory Group, 2018.

3 Jefferds ME, Irizarry L, Timmer A, Tripp K. UNICEF-CDC global assessment of home fortification interventions 2011: current status, new directions, and implications for policy and programmatic guidance. Food Nutr Bull. 2013 Dec;34(4):434-43.

1. What is known about the provision of iron supplements (including MNP) to children at risk of illness from malaria?

A recent Cochrane review on "*Oral iron supplements for children in malaria-endemic areas*" concluded that "iron can be administered without screening for anemia or for iron deficiency, as long as malaria prevention or management services are provided efficiently".[4]

In comparison to children not consuming iron, the review found that children consuming iron supplements (including iron from MNP) are:

- Not at greater risk of becoming infected with malaria
- Not at greater risk of dying
- Less likely to become severely anemic as a result of a malaria episode
- At increased risk of clinical malaria in areas where malaria prevention and management services are not available

While the above outlines the rationale for implementing iron-containing MNP programs in conjunction with measures to prevent, diagnose, and treat malaria for risk-reduction, there is also an additional potential benefit. The review found that the combined approach of providing iron supplementation together with malaria prevention and management reduces both the rates of clinical malaria and anemia among children. Malaria causes anemia through direct destruction of red blood cells. In addition, during illness, the body's inflammatory response prevents optimal absorption of iron, exacerbating anemia. Thus, improved malaria control reduces anemia both by preventing direct red blood cell destruction and improves iron absorption. Simultaneous iron supplementation counters anemia due to malnutrition and iron deficiency.

For these reasons, it is important to ensure that messages promoting consistent insecticide treated bed net use and care seeking for fever are disseminated in malaria endemic areas implementing an MNP program.

2. What is known about ensuring access to malaria prevention, treatment and control programs?

Malaria prevention, often termed vector control, is generally achieved through the use of Insecticide Treated Bed Nets (ITNs) and/or Indoor Residual Spraying (IRS). A well-functioning malaria program will usually have a plan in place to deliver either IRS or ITNs, and occasionally, both interventions are applied. To ensure the population has equitable access to ITNs, the nets are often delivered through periodic mass campaigns (usually at least every 3 years) with some form of continuous distribution in the interim period (i.e., at routine health service contacts such as antenatal care visits, or EPI days). In a limited number of countries, it may be necessary to distribute additional ITNs on a continuous basis (i.e. school-based distribution) to achieve sufficient coverage. Continued behavior change communication on the importance of hanging the nets correctly, and for pregnant mothers and young children to sleep under the nets, is needed. Opportunities to reinforce these messages while counselling families on the use of MNP at home and within the broader community should not be missed as a means to improving malaria prevention and treatment behaviours.[5]

Treatment of malaria is achieved through ensuring access to prompt diagnosis and provision of effective antimalarial drugs. Adequate access to treatment with an effective antimalarial implies that the drug chosen as the first line therapy in the country remains efficacious (>90% effective in in vivo efficacy studies)[6], and that

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4 Neuberger A, Okebe J, Yahav D, Paul M. Oral iron supplements for children in malaria-endemic areas. Cochrane Database Syst Rev. 2016 Feb 27;2:CD006589.

5 Koenker H, Keating J, Alilio M, Acosta A, Lynch M, Nafo-Traore F. Strategic roles for behaviour change communication in a changing malaria landscape. Malaria Journal. 2014;13:1. doi:10.1186/1475-2875-13-1.

6 Artemisinin and artemisinin-based combination therapy resistance. Global Malaria Programme. Status Report. April 2017. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/255213/1/WHO-HTM-GMP-2017.9-eng.pdf?ua=1)

there are sufficient supplies in country and sufficient distribution points that the population can reach these when needed (note that in some hard to reach areas, this may still mean traveling 10-20 km). Ideally, in hard to reach areas, programs will exist, such as community health worker programs (i.e., Integrated Community Case Management, iCCM), to facilitate access to diagnosis and treatment.

Stock-outs of malaria drugs may occur periodically and therefore may temporarily limit access. If there are wide-scale or persistent stock-outs of both the 1st and 2nd line anti-malarials recommended in the country, or of all ACTs, the most effective approach may be to work with the malaria program and the Ministry of Health to discuss the need for a sufficient supply of malaria treatment prior to implementing an MNP program.

3. What is known about the safety of micronutrient powders (MNP) at varying levels of coverage of insecticide treated nets (ITNs) and/or indoor residual spraying (IRS)?

Universal coverage and utilization is ideally what any program seeks to ensure that the population is protected; however, some studies (listed below) with ITN coverage as low as 5-36% did not find increased malaria incidence among the iron-consuming children. These studies, however, were not specifically designed to assess the effect of different ITN coverage levels on iron and malaria risk. The studies below looked at a combination of coverage of ITNs and provision of treatment and found no increased risk in any study, thus reinforcing the need for both prevention control and treatment to be available. In addition, these were all trials in which prompt care seeking for fever was encouraged.

- Veenemans et al. – no impact of daily use of MNP containing folic acid (FA) (93.75µg) and iron (18 mg as ferrous fumarate) on malaria incidence among a rural Tanzanian population (6-60 months of age) reporting 30-36% ITN use when artemether-lumefantrine was given for treatment[7]
- Massaga et al. – iron supplementation in infants (7.5 mg elemental iron/day) was not associated with increased risk for malaria when ITN coverage was about 30% and malaria was treated with sulfadoxine-pyrimethamine[8]
- Menendez et al. – daily oral iron (2 mg/kg body weight daily) was not associated with increased malaria risk where less than 5% of the population were using untreated bed nets and chloroquine was given as treatment for malaria[9]

In 2015, The World Health Organization (WHO) estimated that about 55% of the sub-Saharan African population and 68% of those under 5 years of age slept under an ITN, with better coverage in young children compared to the general population.[10] Studies suggest that the biggest factor in ITN use is access; the majority of young children in households with access to an ITN will sleep under one.[11] However, proper ITN use cannot be guaranteed in all settings. The WHO estimates that, in 2016, only 42% of households in sub-Saharan Africa had sufficient ITNs for all household members, and one-fifth of households did not have access to any nets. MNP can be distributed, along with messages to stress the importance of using an ITN every night and seeking prompt care for fever. Note that in some areas, indoor residual spraying (IRS) may be used either in addition to or in place of ITNs; annual spraying with a long-acting insecticide, in absence of ITN distribution, is considered adequate vector control.[12]

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7 Veenemans J, et al. (2011) Effect of Supplementation with Zinc and Other Micronutrients on Malaria in Tanzanian Children: A Randomised Trial. PLoS Med 8(11): e1001125

8 Massaga JJ, et al. (2003) Effect of intermittent treatment with amodiaquine on anemia and malarial fevers in infants in Tanzania: a randomised placebo-controlled trial. Lancet361(9372):1853–60.

9 Menendez C, et al. (1997) Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anemia and malaria in Tanzanian infants. Lancet 350(9081):844–50.

10 World Health Organization, World Malaria Report 2015 (http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf?ua=1)

11 Koenker H, Kilian A (2014) Recalculating the Net Use Gap: A Multi-Country Comparison of ITN Use versus ITN Access. PLOS ONE 9(5): e97496.

12 WHO guidance for countries on combining indoor residual spraying and long-lasting insecticidal nets. March 2014. Geneva: World Health Organization; 2014 (http://www.who.int/malaria/publications/atoz/who-guidance-combining-irs_llins-mar2014.pdf)

4. What are the WHO recommendations around care-seeking behavior for febrile episodes, feeding of the sick child and treatment of mild, moderate and severe malnutrition?

WHO recommendations state that children who present with any of the following symptoms should seek treatment at the nearest health facility or with the community health worker as soon as possible:[13,14]

- Fever (sweating, feeling cold, and shivering)
- Cough, fast breathing, or difficulty breathing
- Chest in-drawing
- Difficulty drinking or breastfeeding
- Vomiting
- Neck stiffness
- Diarrhea
- Convulsions
- Abnormally sleepy/ unable to wake
- Any other concerns that the child is sick

For breastfed children with malaria, diarrhea, vomiting or pneumonia, it is important that the child continue to breastfeed through the illness. Children may experience reduced appetite during periods of acute illness which can impact optimal feeding of complementary foods; however, as per WHO/UNICEF recommendations, caregivers should be encouraged to continue to offer breastmilk and home-available, age-appropriate foods to children both during and after illness as a means to support recovery.

Only in the case of children who are receiving treatment for severe acute malnutrition using ready-to-use therapeutic foods (RUTF)[15]—whether through an in-patient or out-patient community-based approach— should MNPs be withheld. RUTF products already contain an adequate amount of vitamins and minerals, including iron.[16] Similarly, children who are being treated for moderate acute malnutrition and receiving ready-to-use supplementary foods (RUSF)[17] or Supercereal Plus[18] do not additionally require MNP.

Children with mild-to-moderate malnutrition, if being treated in the community and not receiving RUTF, RUSF or Supercereal Plus, may continue to receive MNP. A community-based randomized controlled trial by Lemaire et al. in Bangladesh found that the use of MNP, along with instructions for appropriate complementary feeding, is safe and efficacious when provided to children aged 12–24 mo. with moderate-to-severe malnutrition and anemia.[19]

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13 http://ccmcentral.com/wp-content/uploads/2014/04/Instructional-and-Pictorial-Job-Aid-for-CDDs-South-Sudan_Malaria-Consortium_2013.pdf

14 WHO, Integrated management of childhood illness: caring for newborns and children in the community.; http://www.who.int/maternal_child_adolescent/documents/IMCI_chartbooklet/en/

15 Ready-to-use therapeutic food (RUTF) are energy dense, micronutrient enhanced pastes used in therapeutic feeding. These soft foods are a homogenous mix of lipid rich foods, with a nutritional profile similar to the World Health Organization-recommended therapeutic milk formula used for inpatient therapeutic feeding programs. Typical primary ingredients for RUTF include peanuts, oil, sugar, milk powder and vitamin and mineral supplements. READY-TO-USE THERAPEUTIC FOOD FOR CHILDREN WITH SEVERE ACUTE MALNUTRITION. UNICEF Positon Paper No. 1. June 2013 . Available at https://www.unicef.org/media/files/Position_Paper_Ready-to-use_therapeutic_food_for_children_with_severe_acute_malnutrition__June_2013.pdf

16 World Health Organization/World Food Programme/United Nations System Standing Committee on Nutrition/The United Nations Children's Fund. COMMUNITY-BASED MANAGEMENT OF SEVERE ACUTE MALNUTRITION. A Joint Statement by the World Health Organization, the World Food Programme, the United Nations System Standing Committee on Nutrition and the United Nations Children's Fund , 2007. Available at: http://apps.who.int/iris/bitstream/10665/44295/1/9789280641479_eng.pdf?ua=1

17 Ready-to-use supplementary food (RUSF) is a food supplement that is intended to be eaten during two to three months, as part of a nutritional program, to treat moderate acute malnutrition for children 6 months and older. Product is intended to be eaten directly from the package with no necessary dilution, mixing or cooking. Available at http://documents.wfp.org/stellent/groups/public/documents/communications/wfp255508.pdf

18 Ibid. Supercereal Plus (previously CSB++) is consumed like porridge by mixing an appropriate proportion of Supercereal Plus and clean water followed by a cooking.

19 Lemaire M, Islam QS, Shen H, Khan MA, Parveen M, Abedin F, Haseen F, Hyder Z, Cook RJ, Zlotkin SH. Iron-containing micronutrient powder provided to children with moderate-to-severe malnutrition increases hemoglobin concentrations but not the risk of infectious morbidity: a randomized, double-blind, placebo-controlled, noninferiority safety trial. Am J Clin Nutr. 2011 Aug;94(2):585-93.

Children identified with severe acute malnutrition with medical complications are typically admitted for in-patient care at a health-facility. In such cases, the WHO recommends not giving iron initially as part of treatment, but to wait until the child regains their appetite and starts gaining weight (usually in the second week).[20]

5. What is known about the relationship between folic acid intake and the efficacy of malaria treatment, given that some of the anti-malaria drugs work by blocking the folate metabolic pathway in mosquitoes?

Sulfadoxine-Pyrimethamine (SP) is used prophylactically to prevent malaria and is a component of the treatment drug - Sulfadoxine-Pyrimethamine- Artesunate (SPAS). SP is an anti-folate drug; sulfadoxine and pyrimethamine synergistically block successive steps in the folate synthesis pathway. High daily doses of folic acid have been shown to interfere with the activity of SP as an antimalarial.[21,22] In pregnant women, studies have shown that low doses of folic acid supplementation, even up to 1.5 mg daily, do not interfere with the efficacy of SP when given prophylactically to prevent malaria (this is known as intermittent preventive treatment in pregnancy, or IPTp), although higher doses (5mg daily) do.[23,24] In children, one study found that a daily dose of 1 mg is sufficient to interfere with the efficacy of SP as an antimalarial[25]; smaller doses have not been studied. Though the data from pregnant women suggests that there is a threshold level of folic acid below which there is not an antagonist effect, a review by Verhoef et al., cautions that "the efficacy of antifolate drugs against Plasmodium is maximized in the absence of exogenous folic acid, so that there may not be a minimum safe dose."[26]

MNP formulated with folic acid typically contain 90 µg folic acid (for children 6—59 months of age) or 180 µg folic acid (for school-age children up to 12 years of age). No studies have looked at the impact of this dose on malaria treatment efficacy specifically, though studies assessing the risk of hospital admission or death have not found an increase among children taking daily doses of 50-260 µg/day, suggesting that at these low doses, there is not a significant impact on SP efficacy. Furthermore, SP should not be used as a single agent for the treatment of clinical malaria; in areas where SP-artesunate is used,[27] the addition of the artesunate component (which acts via a different mechanism) will help ensure high efficacy. In the period from 2013-2015, fewer than 20% of children globally treated for malaria received SP.[28] SP is not advised as a monotherapy, thus, health care workers distributing MNP should emphasize that SP alone is not an effective therapy for malaria, although it may be used in some settings for preventive treatment (i.e., intermittent preventive treatment for malaria in infants (IPTi) or pregnant women (IPTp)). To mitigate such risks, any febrile child living in a malaria endemic area should be tested for malaria regardless of whether they received IPTi or not.

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20 World Health Organization, Management of Severe Malnutrition: A manual for physicians and other senior health workers, WHO, Geneva, 1999, Available at: http://www.who.int/nutrition/publications/en/manage_severe_malnutrition_eng.pdf

21 van Hensbroek MB, et al. Iron, but not folic acid, combined with effective antimalarial therapy promotes haematological recovery in African children after acute falciparum malaria. Trans R Soc Trop Med Hyg 1995;89:672–6.

22 Carter JY, et al. Reduction of the efficacy of antifolate antimalarial therapy by folic acid supplementation. Am J Trop Med Hyg 2005;73:166–70

23 Ouma P, et al: A randomized controlled trial of folate supplementation when treating malaria in pregnancy with sulfadoxine-pyrimethamine. PLoS Clin Trials 2006, 1:e28.

24 Mbaye A, et al: A randomized, placebo-controlled trial of intermittent preventive treatment with sulphadoxine-pyrimethamine in Gambian multigravidae. Trop Med Int Health 2006, 11:992-1002.

25 Mulenga M, et al. Folic acid treatment of Zambian children with moderate to severe malaria anemia. Am J Trop Med Hyg 2006;74:986–90.

26 Verhoef, Veenemans, Mwangi and Prentice. Safety and benefits of interventions to increase folate status in malaria-endemic areas. Brit J Haematology 2017; 177:905-918.

27 SP-Artesunate should only be used in areas where there is not significant resistance of Plasmodium falciparum to SP

28 World Health Organization, World Malaria Report 2016

Contributors

- Julie Gutman, Maria Elena Jefferds, and Katie Tripp, Centers for Disease Control and Prevention (CDC)
- Claudia Schauer and Stanley Zlotkin, Centre for Global Child Health, Hospital for Sick Children, Toronto, Canada
- Aashima Garg and Roland Kupka, UNICEF

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