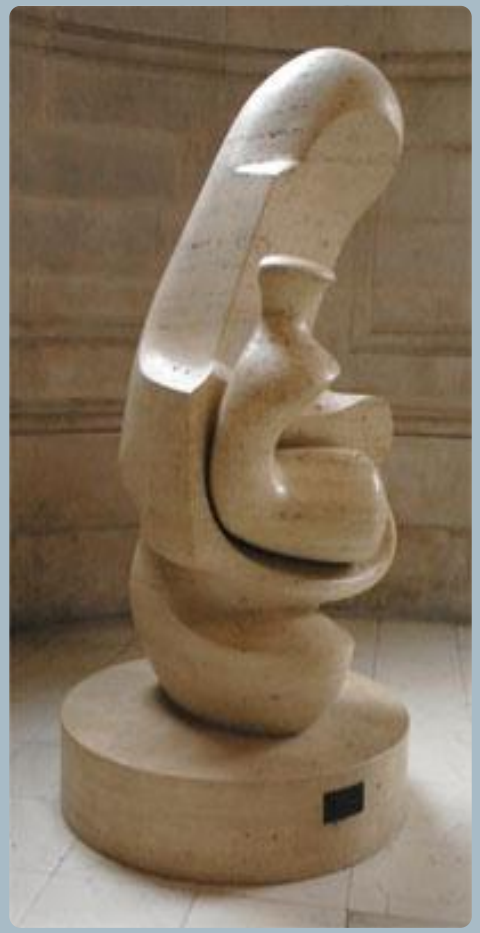

Technologies for Health Consultative Meeting: MNCH Pathways

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MAILING ADDRESS
PO Box 900922
Seattle, WA 98109
USA

ADDRESS
2201 Westlake Avenue
Suite 200
Seattle, WA, USA

TEL: 206.285.3500
FAX: 206.285.6619

www.path.org

Maternal Anemia

USAID FROM THE AMERICAN PEOPLE

PATH A catalyst for global health

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Iron Supplementation and Food Fortification

Consensus exists on a number of evidence-based iron supplementation and food fortification interventions to reduce anemia and micronutrient deficiencies among pregnant women and women of reproductive age.[1] These include universal supplementation of pregnant women with daily iron and folic acid (IFA) tablets and fortification of commonly consumed food products with micronutrients.[2,3] Adequate quantities and types of food and nutrition education are also critical to improving the amount of iron absorbed from the diet and supplements by increasing the intake of iron and especially by improving the bioavailability of iron.[4] In controlled studies, when women were supervised in their pill-taking, iron supplementation was found to be efficacious in preventing and correcting iron-deficiency anemia. Maternal iron and IFA supplementation programs have been ineffective in most countries due to inadequacies in health care delivery systems. These inadequacies have impeded scale-up by failing to get IFA to pregnant women or to provide counseling on why and how to take it. Where attention to supply and demand issues have been put in place, anemia prevalence in women has decreased.[5,6] On a long-term basis, iron fortification is cost-effective at improving the iron status of the entire population, including women before they get pregnant.[7]

The World Health Organization recommends universal supplementation of all pregnant women with a single daily dose of 60 mg of iron for six months in pregnancy or 120 mg of iron if the six-month duration cannot be achieved in populations where gestational anemia is common.[8] In countries where anemia prevalence during pregnancy is high (≥40 percent), women should continue taking IFA for three months after delivery. Programmatically, several factors can limit the effectiveness of iron supplementation interventions, including inadequate political support, lack of program integration with insufficient bundling of interventions, poor supply management and inadequate supplies, low utilization and lack of demand for antenatal care, insufficient adherence counseling, non-adherence among mothers, cultural issues and taboos, inadequate community involvement, weak systems for program monitoring and evaluation, and lack of convincing evidence of effectiveness.

Available literature from several countries suggests that the most important reason for the failure of supplementation programs is a lack of supplies, but non-adherence on the part of pregnant women can also be a significant factor.[9,10] Research from eight counties found that a primary reason women were not taking IFA was because they had not received iron pills through the health system.[11] This was due to a number of factors, including women's late attendance for antenatal care and lack of supplies. Most women took their IFA when they had adequate counseling. For practical and cultural reasons, women preferred pills that were small, red, film-coated, and with protective packaging. Some women missed doses or did not take all the IFA they received because they forgot to take them or due to the difficulty in taking any medication over the long term. In addition, even though evidence exists of iron supplementation programs for about 50 countries, given the multiple

etiologies of anemia, secular trends, and concurrent interventions, the proportion of anemia reduction attributable to iron supplementation has not been adequately quantified.[12] Evidence from well-designed and well-implemented iron supplementation programs is needed to demonstrate program effectiveness and impact in real-world settings. Furthermore, to date, many large-scale iron fortification programs have failed to demonstrate a measurable impact on anemia prevalence because they used iron fortificants with low bioavailability and/or because consumption by the at-risk population was low. More evidence is needed from iron fortification programs using bioavailable forms of iron.

In addition to iron tablets, iron-folate combination tablets are available. Iron-fortified foods include salt, sugar, rice, flour, milk, coffee/tea, juice, water, condiments, cereals, biscuits, and bread rolls, among many others. The table below outlines six supplementation and fortification opportunities.

Supply Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Description of technology	Oral ferrous sulfate or ferrous fumarate tablets in various forms, which can affect adherence: e.g., white, brown, red in color; different sizes; separate or combined iron-folic acid; film or chalk coated.	Ferrous sulfate incorporated into a hydrocolloid matrix that becomes buoyant on exposure to gastric secretions; thus, the gastric delivery system is retained for prolonged periods in a soluble form in the acidic environment of the stomach and iron absorption is possible with smaller doses.	This breakthrough technology allows salt to be double fortified with iron as well as iodine.	Flour is commonly fortified with iron, zinc, folic acid, and other B vitamins such as niacin and riboflavin.	Rice fortification technology is a culturally appropriate and cost-effective micronutrient delivery system that packs vitamins and minerals into extruded rice grains made from rice flour. Ultra Rice® (UR) and NutriRice™ (NR) resemble milled rice in size, shape, and color. When blended with milled rice (often at a 1:100 ratio), the resulting fortified rice is nearly identical to traditional rice in smell, taste, and texture.	Microencapsulated micronutrient powder that contains iron, folic acid, and calcium. Sprinkles powder is packaged in individual single-dose sachets and is easily sprinkled on any foods prepared in the home, providing instant fortification. Coating of the iron prevents changes to the taste, color, or texture of the food to which Sprinkles is added.
Technology characteristics applicable for low-resource settings (e.g., no need for power supply)	Multiple manufacturers and in-country suppliers. Thermostable and broad safety profile.	Potential for increased absorption with smaller doses, reducing side effects.	Stable during storage and transportation. Bioavailable. Acceptable and safe to consumers. Effective in reducing iron-deficiency anemia.	Commonly used commodity.	The UR and NR formulations can carry a range of micronutrients, including vitamin A, iron, zinc, thiamin, and folic acid.	Encapsulation of the iron source (ferrous fumarate) prevents interaction with food (unacceptable metallic aftertaste and change in color, smell, or texture). Easy to use by anyone on any food item.
Developer and/or manufacturer of the technology/ intervention	Various.	Eli Lilly.	Micronutrient Initiative.	Various.	UR: PATH. NR: DSM/Bühler partnership.	Developed by researchers at the Hospital for Sick Children in Toronto. The Sprinkles Global Health Initiative is the nonprofit entity. Not yet commercially available.

Supply Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Status of technology	Commercialized.	Developed by Eli Lilly in the mid-1990s at the request of the United States Agency for International Development, but not scaled up due to concerns regarding market demand.	Transferred to manufacturers for commercialization.	Broad-scale usage in developed countries; planned or voluntary adoption in many developing countries.	UR: In India, PATH transferred the UR technology to Swagat Foods in 2008 and has license agreements with other entities. In 2010, the world's largest school lunch program incorporated UR into its centralized kitchens in Rajasthan, serving 185,000 children daily. In 2009, PATH and the Naandi Foundation pursued a similar pilot, reaching 60,000 school children daily in Andhra Pradesh. In Brazil, PATH transferred the UR technology to Adorella Alimentos in 2009, and school lunch programs with UR reach 55,000 children daily. In Burundi, PATH (in partnership with World Vision) will soon reach 15,000 school children daily through a meal program supported by the World Food Programme (WFP). PATH aims to improve the micronutrient status of these children and generate further operational and biological impact data—expanding the evidence base for UR and building the case for inclusion on the commodity lists of the two largest food aid suppliers, the United States government and WFP. NR: Commercially available in multiple countries as fortified rice premix.	Pilot studies have been conducted. A prenatal Sprinkles study in Bangladesh is planned to start 12–18 months from July 2011. Commercialization efforts are on hold. Exploring manufacturing and distribution partnerships in North America and in developing countries in both the private and public sectors.

Supply Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Efficacy/ effectiveness	Highly effective when the patient is adherent.	There is no meta-analysis, and evidence is too scarce to provide conclusive data on the efficacy and effectiveness of the gastric delivery system in pregnant women.	Has been demonstrated to be effective in reducing iron-deficiency anemia.	Has been demonstrated to be effective.	UR: UR has been intensively studied to ensure it is efficacious, shelf stable, and acceptable to consumers. Twenty-eight studies to date in eight countries form the evidence base for UR. NR: Studies to determine the efficacy of NR have been conducted in China and India over 6–8 month periods. Results showed a reduction of the effects of malnutrition by 50 percent.	The majority of studies have been conducted with infants/children and have shown Sprinkles to be as efficacious as standard oral iron drops. Sprinkles sachets taken once daily for 60 days were effective in improving hemoglobin levels and reducing the prevalence of anemia. There is a special formulation of Sprinkles for pregnant/lactating women; studies with pregnant women are needed to determine efficacy.
Manufacturing	Multiple suppliers exist for this technology category, suggesting that additional capacity to meet potential demand increases exists within the existing system.	Not currently manufactured.	Technology transfer to multiple salt producers to allow the technology supply capacity to expand with demand.	Technology transfer to multiple flour millers to allow for the technology supply to grow with demand.	UR: To establish supply, PATH partners with local pasta manufacturers to produce the UR grains, and then works with rice millers and public-sector feeding programs to blend and distribute the fortified rice. These strategies maximize the opportunity for fortified rice to be operationally feasible, affordable, and accessible at the local level. NR: DSM and Bühler are large, well-established, multinational companies. They jointly own a NR production facility in China.	Not currently commercialized or manufactured. Product available only for pilot investigation (e.g., for planned pilot in Bangladesh). The Hospital for Sick Children and the Sprinkles Global Health Initiative are currently partnering with private-sector companies.

Supply Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Intellectual property (IP) ownership	Generic.	Unknown if formulation is in the public domain.	Micronutrient Initiative.	Data not available.	UR: PATH. NR: DSM/Bühler partnership.	The IP rights to Sprinkles are owned by Ped Med, Ltd., a private incorporated company owned by Dr. Stanley Zlotkin.
Cost and cost drivers	Extremely low cost and often provided to patients free of charge. Cost drivers are driven by formulation of iron used. Packs of 1,000 tablets supplied by the United Nations Children's Fund range from US$3.00 to US$5.40.	Unknown, but assumed that it was not seen to be cost competitive with the status quo option, or the value proposition was not strong enough to justify the premium.	The cost of adding iron to iodized salt is about US$0.06 per kg of salt. Costs will decrease as greater volumes of premix are produced.	Miller profit margins are sometimes low. Attempts to increase profit margins through premium pricing of fortified products result in products likely to be affordable by only a small proportion of the population in most countries. For a staple like wheat flour, everyone is concerned about price. Governments, commercial customers, and consumers want it low; competition drives it down since there is little or no real product differentiation.	UR: Local production and distribution of UR helps to minimize costs. PATH is also facilitating the identification and acquisition of low-cost blending equipment for rice millers to blend UR with their rice supplies. Overall, UR adds 3 to 5 percent to the cost of traditional rice. NR: Unknown, but NR is aimed at high-end market consumers.[13]	The cost of producing Sprinkles is between US$0.03 and US$0.05 per sachet, depending on the volume that is produced.

Supply Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Delivery/ procurement channels	Delivery and procurement is through standard in-country medical supply channels.	If commercialized, would use standard in-country medical supply channels.	Delivery and procurement strategy is to use existing salt supply channels and manufacturers.	Delivery and procurement strategy is to use existing flour miller supply channels.	UR: Rice millers and public-sector feeding programs are primary distribution channels for UR. It is also sold at Fair Price Shops (part of India's Public Distribution System). NR: The primary procurement channel is for rice millers targeting consumer end users.	Sprinkles is primarily a consumer-packaged good. Subsidization and distribution through the public sector and community-based distribution channels would be necessary to drive adoption.
Sustainable business models	Commodity product with multiple suppliers, suggesting sustainable margins with existing business.	Would need to be developed.	Additional product line for salt manufacturers. Likely will need initial subsidization to demonstrate effectiveness and acceptance.	A level playing field is essential. Countries are recognizing that a "mandatory" approach is the only effective way forward. However, they are using a variety of mechanisms (law, regulation, standard) and euphemisms (universal, quality standard) to achieve this.	UR: Production partners are contractually committed to limiting their profit margin when selling fortified rice to public-sector programs. NR: DSM/Bühler is interested in an export model (producing at scale in China and exporting), although they have considered additional plant investments in India and other large markets.	Business models not yet determined.

Demand Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Existing demand	World Health Organization (WHO) guidelines and many country guidelines require the use of supplements for all pregnant women. Market size is driven by the number of pregnant and postpartum women. All pregnant women should receive iron supplementation pills, and postpartum women who are iron deficient or at risk should be given oral supplements.	WHO guidelines and many country guidelines require the use of supplements for all pregnant women. Market size is driven by the number of pregnant and postpartum women who fail to adhere to oral iron tablets. All pregnant women should receive iron supplementation pills, and postpartum women who are iron deficient or at risk should be given oral supplements.	Demand-generation activities in India and Bangladesh are ongoing. Demand drivers are population-wide supplementation.	Sixty-four countries currently have legal requirements for fortification of at least one type of wheat flour with at least iron and/or folic acid. Globally, 30 percent of flour from large-roller mills is fortified, and the remaining 70 percent represents potential to improve the lives of millions of people. Broadly speaking, the market size is driven by population-based fortification strategies.	UR: Demand-generation activities in India, Brazil, and China are ongoing. In Brazil, PATH is working on building commercial retail channels with some of the country's largest millers and retailers. The goal is to hit 10 million consumers in three years. In India, PATH will pilot UR in three districts of Andhra Pradesh starting in January 2013, likely reaching about 200,000–400,000 consumers over the year via distribution through Fair Price Shops. NR: The existing demand for imported fortified rice product is currently unknown. PATH and DSM/Bühler are currently working together in India and Brazil on market growth activities. Market size is driven by population-based fortification strategies.	Market size is driven by the number of pregnant women with low dietary intake of iron and who have hemoglobin levels below acceptable cutoffs. Postpartum women who suffered blood loss should also be provided with food supplements. Broadly speaking, the market size for this technology includes pregnant and postpartum women who may be iron deficient.
Attractiveness	Iron pills are low cost and effective when used as directed. Gel tablets are easier to swallow. Side effects reduce the attractiveness of the pills and affect adherence.	The reduced dosage would potentially improve adherence, but increased cost may limit availability.	High attractiveness, as salt is a regularly used commodity. Increased cost and the need to mix or blend double-fortified salt would be a barrier that slows adoption.	High attractiveness. Flour is a widely used commodity and often subsidized.	High attractiveness. Rice is a widely used commodity. These technologies do not affect the smell or taste of rice or method of cooking. Barriers include overcoming costs.	Easy to use and minimal side effects. Studies showed strong evidence that Sprinkles is highly acceptable to end users, but that a low or subsidized cost would be necessary for adoption. Differential time-released nutrients help with iron and other deficiencies.

Demand Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Price sensitivity	Procured by the public sector for free distribution. Often, the lowest-cost product is chosen over the side-effect profile.	Procured by the public sector for free distribution. Often, the lowest cost product is chosen over the side-effect profile.	Salt is a commodity, so consumers are likely to be price sensitive.	High consumer and public-sector sensitivity to price differences.	UR: To date, pilot introductions in India have demonstrated that the integration of UR into school lunches provided by centralized kitchens costs an estimated US$0.41 per school year, per child. Fortified with UR grains, the lunches provide children with half of their recommended daily allowance of iron. This price point makes integration of UR within existing school lunch programs an extremely affordable health intervention compared to alternatives. NR: The additional premium placed on imported fortified rice is not currently known, nor has any NR market research with regard to consumer sensitivity been made publically available.	Studies demonstrated that consumers are price sensitive, and a strong value proposition and awareness campaign would be necessary to drive adoption.
Policy environment	Many donors and organizations have championed iron supplementation—WHO, United Nations Children's Fund, United States Agency for International Development (USAID), Micronutrient Initiative, etc.	USAID has shown interest in the past. WHO is interested in investigating further.	WHO recommends supplementation for all pregnant women.	WHO recommends supplementation for all pregnant women.	WHO recommends supplementation for all pregnant women.	WHO recommends supplementation for all pregnant women.

Demand Information	TECHNOLOGY/SOLUTION					
	Iron tablets	**Gastric delivery system**	**Iron-fortified salt**	**Iron-fortified flour**	**Ultra Rice®/NutriRice™**	**Sprinkles**
Donors/ stakeholders	Donors and stakeholders have supported iron supplementation programs through programmatic support and availability.	USAID is interested in the potential of this technology.	This intervention has the support of the Micronutrient Initiative and the University of Toronto, with financial support from the Canadian International Development Agency and the World Bank.	This intervention has the support of the Flour Fortification Initiative.	UR: The Bill & Melinda Gates Foundation and other donors have supported work around development, manufacture, clinical studies, and commercialization. NR: In 2011, DSM/Bühler announced partnerships with USAID and the World Food Programme, and received an award for the most innovative rice fortification product from the Global Alliance for Improved Nutrition and the International Business Leaders Forum.	The University of Toronto has been the major driver of the technology. Sprinkles received a grant award from Saving Lives at Birth: A Grand Challenge for Development in 2011.
Pre- and post-sales support	Would need a consistent last-mile supply chain.	Would need a consistent last-mile supply chain.	Pre-sales support to salt producers for equipment and training.	Training to flour millers for fortification steps.	Training and technology transfer to rice millers, and ongoing supply of fortified rice.	The product is a consumer packaged good and does not require pre- or post-sales support.
Need for demand creation	Need to generate awareness among patients with regard to the risk of anemia and benefits of supplementation.	Yes, to demonstrate cost-effectiveness.	Yes, to drive adoption by the public sector and consumers.	Support advocacy work by the Flour Fortification Initiative.	Yes, to continue to drive adoption by the public sector and consumers, PATH and DSM collaborated in India and jointly submitted an application to the Food Safety and Standards Act of India. In Brazil, they jointly developed a logo to support food fortification.	To reinvigorate product development, activities focused on demand creation would be critical to drive adoption.

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Hemoglobin Measurement

Hemoglobin (Hb) is an oxygen-carrying protein in red blood cells that binds oxygen through its iron component. Hemoglobin, expressed as the amount of Hb in grams (g) per deciliter (dl) of whole blood, is a common indicator for diagnosing anemia and is relatively easy to determine. The normal ranges of Hb depend on age and gender. World Health Organization (WHO) ranges for pregnant women that guide the level and kind of intervention needed are identified as follows: mild anemia—Hb level of 10.0 g to 10.9 g/dl; moderate anemia—Hb of 7.0 g to 9.9 g/dl; and severe anemia—Hb of less than 7.0 g/dl.[1] Due to the high prevalence and known complications of anemia during pregnancy, screening for anemia is recommended at least once during antenatal care visits in most developing countries.[2] WHO supports screening prior to iron supplementation if anemia prevalence is <20% and protocols and guidelines for action are available.[3] However, in most developing countries, there are no supplies for hemoglobin tests so most women are not screened. In many settings, anemia is identified using clinical screening which, though qualitative, is fairly sensitive in screening for severe anemia but not mild and moderate anemia.[4]

While there is consensus that iron deficiency should be prevented through a range of primary prevention methods, there is less evidence and agreement regarding whether screening is necessary, and if so, how best to do that. The problem is further complicated by the absence of a reliable, sensitive, low-cost, rapid test for Hb measurement and the lack of evidence that specifically addresses the accuracy of screening tests in asymptomatic pregnant women. However, there is agreement that early screening could help identify women who need special care and monitoring and women who are at high risk and could benefit from early intervention. A recent meta-analysis[5] shows that mild and moderate—not just severe—anemia has serious consequences for women, which supports previous estimates that correcting anemia of any severity reduces the risk of death; the risk of maternal mortality decreases by about 20% for each 1 g/dL increase in Hb.[6] This is a new finding and different from the earlier view that only severe anemia is associated with increased mortality. It has important policy and program implications. Country programs will need to consider their disease burden, the resources available to them, and their overall strategy in determining whether larger screening efforts for maternal anemia are justified.

The choice of screening tools for Hb estimation depends on the purpose of the assessment and the resources available. The most widely used tests for Hb measurement among pregnant women are the simple, low-cost, semiquantitative tests such as the Sahli method and the WHO hemoglobin colour scale (HCS), using filter paper. These tests are relatively simple to use and low cost, but they rely on subjective color matching and give ranges for Hb levels rather than specific numeric measurements. The HemoCue® is easy to use and accurate, but requires a disposable cuvette; as a result use of the HemoCue in developing countries for screening is limited because of the relatively high cost of the cuvettes. The

device is used mainly for population surveillance and monitoring. The laboratory-based automated analyzer tests require collection of a venous blood sample with the associated requirements for sterile equipment, disposable blood-draw supplies, trained technicians, and disposal of contaminated samples and sharps. Therefore, purchasing and using these devices is expensive, and they are used mostly in tertiary facilities or facilities that are equipped with laboratories. Clinical detection of anemia by examination for pallor is also widely used; it is only effective at identifying severe cases of anemia and is not sensitive as a measure for identification of mild to moderate anemia and thus could miss many cases of iron-deficiency anemia. Recent development of noninvasive technologies that use a simple finger probe and are based on infrared spectrophotometry could provide alternative tools for Hb estimation. The noninvasive devices provide a safer and easier method of Hb measurement. Such new methods—if sufficiently accurate and cost-effective—could expand access to screening and facilitate population surveillance and monitoring efforts.

The two tables below examine twelve technologies/solutions for hemoglobin measurement.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Clinical signs	**Hemoglobin colour scale**	**Sahli**	**HemoPoint®**	**HemoCue®**	**Pronto®/Pronto-7™**
Description	The inner eyelid, lips, tongue, gums, and the area under the fingernails are examined and the degree of pallor indicates the severity of anemia.	The Hemoglobin colour scale (HCS) uses a capillary blood sample that is collected directly onto a strip of filter paper and compared to a set of color standards. The test provides a scale for Hb ranges that coincide with the WHO cutoff levels.	The Sahli method is based on converting hemoglobin to acid hematin and then visually matching its color against a solid glass standard.	Optical absorption photometry based on the azidemethemoglobin principle.	A handheld, point-of-care device. A small amount of capillary blood is wicked into a disposable treated cuvette that is inserted into the device and provides a Hb value that is digitally displayed in g/dl. Uses optical absorption photometry based on the azidemethemoglobin principle.	The Pronto and Pronto-7 are point-of-care devices that use a finger probe to detect total hemoglobin. The devices expand the capability of Masimo's pulse oximeter to include quantitative measurement of blood Hb.
Characteristics applicable for low-resource settings	No blood sample is required. No consumables or technology needed. Fits well at the community level where blood draws are not feasible and/or where cultural barriers exist around blood draws.	No power supply is required or kinetic or chemical reaction. The only consumables are the filter paper strip and lancet. It can be used by minimally trained workers.	No power supply is required. Requires recurring supply of dilution solution. Does not require a trained lab technician for use. Portable and low cost.	Rugged, portable, and accurate point-of-care hemoglobin meter. Requires use of a disposable cuvette.	Rugged, portable, and accurate point-of-care hemoglobin meter. Requires disposable cuvettes. Easy to use; provides clear digital result in less than one minute.	Noninvasive, portable, limited consumables (probe), and requires limited training. Easy to use; provides clear digital result in 30 to 90 seconds.
Developer and/or manufacturer	Not applicable.	Developed by WHO; licensed to CoPack for manufacturing. www.copackservice.de.	Various manufacturers and suppliers.	Stanbio (acquired by EKF Diagnostics in 2011). www.stanbio.com	HemoCue AB (acquired by Quest Diagnostics in 2007). www.hemocue.com	Masimo. www.masimo.com

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Clinical signs	**Hemoglobin colour scale**	**Sahli**	**HemoPoint®**	**HemoCue®**	**Pronto®/Pronto-7™**
Status	Broad adoption. Used widely as a screening method at peripheral facilities.	Commercially available through the UNICEF Supply Catalogue, and the Maternova, CoPack, and Teaching Aids for Learning websites. Market penetration is low, as this technology is not widely available through private-sector supply chains nor has it been widely adopted by the public sector.	Commercially available. De facto standard in community settings.	Commercially available.	Commercially available. Relatively familiar in low-resource settings. Used most extensively for population surveillance and monitoring.	Commercially available. Marketing efforts are currently focused on developed-world applications. Products are CE and US Food and Drug Administration (USFDA) approved.
Efficacy/ effectiveness	Sensitivity: 64% in severe anemia. Specificity: 70%–100%. Not as sensitive for mild and moderate anemia.	Studies conducted on the HCS in several countries in the mid-1990s found overall sensitivity was 96% and specificity was 86%. A systematic review in 2005 indicated sensitivity ranged from 76% to 88% and specificity ranged from as low as 33% up to 85%. For severe anemia, sensitivity ranged from 50% to 94% with specificity ranging between 86% and 99%.	Sensitivity: 85% Specificity: 85%	Stanbio's 510(k) Substantial Equivalence Determination indicated equivalence to HemoCue®.[7] Therefore: Sensitivity: 85% in field settings, and 100% in laboratory. Specificity: 94%.	Sensitivity: 85% in field settings, and 100% in a laboratory. Specificity: 94%.	Between 6 g and 18 g/dL; greater than 95% of SpHb readings were within 1 g to 2 g/dL of laboratory value.
Manufacturing	Not applicable.	Demand for this technology has not materialized over the last decade of commercial availability, so it is unknown if the manufacturer has the capacity to meet the full demand potential. Annual sales were at about 15,000 in 2009.	Various manufacturers currently operating to meet demand for supplies needed for Sahli method.	Unknown specific manufacturing capacity. In 2011, Stanbio became part of the EKF Diagnostics Group, a family of international companies. Stanbio follows international quality assurance and regulatory compliance standards.[8]	Unknown specific manufacturing capacity but likely could scale with increased demand. In 2007, HemoCue was acquired by Quest Diagnostics. HemoCue follows international quality assurance and regulatory compliance standards.[9]	Likely high ability to meet potential demand as the manufacturer exports products globally. Devices meet international quality assurance and regulatory compliance standards; CE and USFDA approved.[10]

Supply Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Clinical signs	**Hemoglobin colour scale**	**Sahli**	**HemoPoint®**	**HemoCue®**	**Pronto®/Pronto-7™**
Intellectual property ownership	Not applicable.	WHO; licensed to CoPack in 2000.	Likely off patent.	Stanbio.	HemoCue AB.	Masimo.
Cost and cost drivers	No cost.	UNICEF catalogue starter kit: US$28.09 for 1,000 test strips (~US$0.03 per test), instructions, booklet, and dispenser.[11] UNICEF catalogue refill kit: US$44.57 for 2,000 test strips (~US$0.02 per test). Also to be considered are the recurring costs of lancets and supplies for safe use/disposal.	The test kit costs ~US$20. Cost per test is estimated to be ~US$0.15/test.	The device costs ~US$1,000; cost per test is ~US$1.32.	The device costs ~US$350 to US$547; cost per test is ~US$0.87.	Device cost is approximately US$1,200. Cost per test ranges from US$2 to US$8 in developed countries (reimbursable). Low-resource setting costs not yet available.
Delivery/ procurement channels	Not applicable.	Appropriate for community and small clinic settings. Supply and distribution for this product is challenging. Currently it is available through UNICEF and the Maternova, CoPack, and Teaching Aids for Learning websites. But health providers in the field have indicated that availability is limited.	Appropriate for community and small clinic setting. Procurement exists through standard medical supplies channels.	Appropriate for community and small clinic setting, wards in larger facilities, and demographic surveys. Unknown procurement channels in developing countries.	Appropriate for community and small clinic setting, wards in larger facilities, and demographic surveys. Procurement exists through standard medical supplies channels and the UNICEF Supply Catalogue.	Potentially appropriate for community and small clinic setting, wards in larger facilities, and demographic surveys. Masimo has distributors in the United States, Asia, Europe, and the Middle East.
Sustainable business models	Not applicable.	A public-private partnership was created to sustainably provide this technology.	Technology has been the standard practice in many low-resource settings for decades.	Dual market. Device created for developed-world markets; also available (generally without subsidy) to developing-world markets.	Dual market. Device created for developed-world markets; also available (generally without subsidy) to developing-world markets.	Masimo is a profitable public company with revenue >US$300 million. Modified business models for developing-country and public-sector markets needed.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Clinical signs	**Hemoglobin colour scale**	**Sahli method**	**HemoPoint®**	**HemoCue®**	**Pronto®/Pronto-7™**
Existing demand	Standard practice in clinical training. Used widely at peripheral centers as a method to screen for severe anemia. Demand driver is new training of health care providers. Especially important for frontline health workers.	There is currently existing demand for an accurate, low-cost anemia screening tool for antenatal care (ANC) where the infrastructure does not exist to support a hematology analyzer. Potential buyers are ministries of health (MOH), nongovernmental organizations (NGO), and private clinics for use by nurses and frontline health workers. Demand drivers are dependent upon number of community facilities and community-based frontline health workers conducting anemia screening or ANC clinics.	Demand exists by MOH and local NGOs for use at primary health and rural clinics. Existing demand is driven by settings where infrastructure and financial resources do not exist to support a hematology analyzer. Demand drivers are dependent upon number of community facilities and community-based frontline health workers conducting anemia screening or ANC clinics.	Unknown; likely a competitor to HemoCue. Demand drivers are dependent upon number of community facilities with consistent or intermittent power and frontline health workers with occasional access to electricity conducting anemia screening or ANC clinics.	Primary market for low-resource settings is demographic survey organizations (i.e., Demographic Health Service/Macro). Primary health clinics and rural facilities would use it for screening. The key barrier is high recurring cost of cuvettes. Demand drivers are dependent upon number of community facilities with consistent or intermittent power and frontline health workers with occasional access to electricity conducting anemia screening or ANC clinics.	MOH and private-sector clinics without the infrastructure or resources required for a hematology analyzer. The priority market segments are women coming in for antenatal and postnatal services. Other users would be community outreach campaigns, blood donation, nutrition population surveillance, child health programs, and emergency obstetric care. Demand drivers are dependent upon the number of community facilities with consistent or intermittent power and frontline health workers with occasional access to electricity conducting anemia screening or ANC clinics.
Attractiveness	Only accurate for moderate to severe anemia. Not quantitative.	Simple to use, quick, can be used at point of care Accuracy is the greatest barrier to use. Sensitivity and specificity are both 60% at 10 g/dl.	Simple to use, portable, and does not require power. Can be used at point of care.	Medium attractiveness. Accurate, simple to use, and portable. High recurring costs.	Medium attractiveness. Accurate, simple to use, and portable. High recurring costs.	Device is simple to use, and noninvasive nature is viewed as a significant advantage. Still needs to be validated for accuracy and readiness for field use.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Clinical signs	**Hemoglobin colour scale**	**Sahli method**	**HemoPoint®**	**HemoCue®**	**Pronto®/Pronto-7™**
Price sensitivity	Not applicable.	Low cost, at between US$0.10 to US$0.12 per test makes it very attractive for low-resource settings. Also to be considered are the recurring costs of lancet and supplies for safe use/disposal.	Sahli method is the de facto standard in community settings and cost estimates in India range from US$0.06 to US$0.10.	Rural clinics are especially price-sensitive to recurring costs and anchor to the cost of the Sahli method, which is well below the cost of HemoPoint®.	Rural clinics are especially price-sensitive to recurring costs and anchor to the cost of the Sahli method, which is well below that of the HemoCue®.	Rural clinics are especially price-sensitive to recurring costs and anchor to the cost of the Sahli method, which is well below that of the Masimo devices.
Policy environment	Current standard of practice.	In 2004, WHO convened a consultative group to look at increasing access and reducing barriers to wider dissemination. USAID supported earlier development efforts and more current analysis of issues impeding use.	There are no policies that would stand in the way of increased use.	No known policies or studies would stand in the way of the use of this device.	No known policies or studies would stand in the way of the use of this device.	No known policies or studies would stand in the way of the use of this device.
Donors/ stakeholders	Not applicable.	UNICEF, WHO, and USAID/PATH/HealthTech have previously been key technology champions.	None known.	None known.	Donors from around the world have invested in supporting studies and the use of the HemoCue for Hb estimation.	Finalist in the Saving Lives at Birth 2011; interest in a noninvasive screening technology is high. PATH is working with Masimo to determine usability of device and viable business models
Pre- and post-sales support	Not applicable.	Initial training is required, but no post-sales support is necessary beyond recurring purchase of consumables.	Initial training is required, but no post-sales support is necessary beyond recurring purchase of consumables.	Initial training is required. Recurring purchase of consumables and occasional maintenance required.	Initial training is required. Recurring purchase of consumables and occasional maintenance required.	Initial training on the device for proper usage and replacement of probes is required.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 1					
	Clinical signs	**Hemoglobin colour scale**	**Sahli method**	**HemoPoint®**	**HemoCue®**	**Pronto®/Pronto-7™**
Need for demand creation	Not applicable.	Efforts to build awareness about the need for screening would drive adoption.	Efforts to build awareness about the need for screening would drive adoption.	Efforts to build awareness about the need for screening would drive adoption.	Efforts to build awareness about the need for screening would drive adoption.	Noninvasive devices have a significant advantage over existing screening methods. Further local accuracy and field studies are needed to generate demand.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2					
	TouchHb	**Haemospect®**	**NBM-200MP**	**Hematocrit-centrifuge**	**Hematology analyzer**	**Multiplex anemia etiology tool**
Description	Biosense is developing a portable, noninvasive device optimized for low-resource settings to provide total hemoglobin, oxygen saturation, and pulse rate.	The Haemospect® is a handheld, portable device that includes a battery-driven measurement device, a measurement probe, and a holder in which the device is recalibrated. It was originally designed for continuous measurements of six key indicators. Individual point-of-care measurements are now possible. The device is powered by batteries and uses a button sensor that adheres to the palm side of the finger.	NBM-200MP can measure absolute blood (Hb). It is a device that monitors and displays total Hb, oxygen saturation, low-signal oximetry, pulse rate, plethysmogram—all noninvasively and continuously. The system is designed for use in hospitals including operating and recovery rooms and intensive care units as well as in outpatient sites and emergency services.	The hematocrit level or packed-cell volume is a measure of the ratio of the volume of red cells to the total volume of whole blood (plasma, white blood cells, and red blood cells) and is expressed as a percentage. The ratio is determined after centrifugation. The hematocrit level is approximately three times the hemoglobin level.	The features of Abbott Cell Dyn 4000 analyzer include fully automated monoclonal antibody testing, fully automated reticulocyte analysis, fluorescent DNA staining of nucleated red blood cells, optical and impedance platelet measurement, autoloader with multiple type tube capacity, five-part leukocyte differential, 106 samples per hour, and walkway automation with 41 parameters. Using less than 120 µL of sample, you can measure up to 110 complete blood counts per hour with this analyzer.	Claro Scientific has developed SpectraWave™, a point-of-care medical diagnostic system requiring a drop of blood to conduct a comprehensive patient analysis. Claro applied its patented photonics-based technology to develop this innovative diagnostic product platform system. The system optimizes the capture of how light interacts with a sample. The result is an optical profile, a highly quantitative data file used for sample identification, characterization, and quantification. Proprietary models and algorithms analyze the optical profile to characterize the sample including the size, shape, chemical composition, and internal structure of cells and particles.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2					
	TouchHb	**Haemospect®**	**NBM-200MP**	**Hematocrit-centrifuge**	**Hematology analyzer**	**Multiplex anemia etiology tool**
Characteristics applicable for low-resource settings	Noninvasive, portable, limited consumables (probe), and requires limited training.	Noninvasive and portable with limited consumables (probe).	Noninvasive with limited consumables (probe).	Method does not require lysing or dilution of blood and can run multiple samples at the same time. No recurring costs or consumables; results in 4 to 5 minutes.	Gold standard for accuracy, provides full blood panel, and samples can be stored and batched; automated options available. However, analyzers require infrastructure (power, supply chain for reagents, maintenance) and are not portable.	Single-sample analysis replaces several tests, and comprehensive results available within 5 minutes; fully automated; does not require skilled lab technician; nearly reagentless; low cost to operate; durable components, minimal maintenance; scalable for using the same technology in laboratories; new tests can be added through remote updates.
Developer and/or manufacturer	Biosense (www.biosense.in).	MBR Optical Systems (www.mbr-optical-systems.com).	OrSense, Inc. (www.orsense.com).	Various.	Various (example: Abbot Cell Dyn 4000).	Claro Scientific (PATH in collaboration for this etiology tool).
Status	Currently under development. Alpha product available for accuracy and field evaluation. Beta design expected in March 2012.	Commercially available. Marketing efforts are currently focused on developed-world applications.	Commercially available. Marketing efforts are currently focused on developed-world applications.	Commercially available and found in many lower-level facilities equipped with laboratories.	Commercially available. Multiple manufacturers exist and distribute to developing-world markets.	Early stage in development.
Efficacy/ effectiveness	Accuracy studies still underway.	No data available.	Unknown, but the company reports that the device has been validated in developed-country settings with over 4,000 patients.	Sensitivity is greater than 90% if centrifuge speed is consistent.	The gold standard. Sensitivity: 100% Specificity: 90%	To be determined.

Supply Information	TECHNOLOGY/SOLUTION—TABLE 2					
	TouchHb	**Haemospect®**	**NBM-200MP**	**Hematocrit-centrifuge**	**Hematology analyzer**	**Multiplex anemia etiology tool**
Manufacturing	Biosense is currently building capacity for manufacturing. Short-term strategy is to have the electronics manufactured in Germany and assembled in India.	Manufacturing capacity is unknown, but MBR is a global company with distributors in nine regions and likely can scale to meet demand.	Manufacturing capacity is unknown. OrSense is still a young company and may need additional resources to scale to meet global demand.	Various manufacturers available to provide devices. Centrifuges are standard lab equipment.	Various manufacturers exist and could potentially meet demand.	Manufacturing processes are currently being evaluated.
Intellectual property ownership	Biosense.	MBR.	OrSense.	Commodity technology.	Various proprietary technical design elements.	Algorithms are proprietary to Claro Scientific.
Cost and cost drivers	Not yet finalized; it is likely to be ~US$200 per device and ~US$40 per replacement probe (=1,000 tests).	The cost of the Haemospect is approximately US$8,159 (€6,200).	Pricing is not available.	The device cost is US$200; recurring costs are lancets and capillary tubes.	The analyzer costs US$5,280 to US$60,000; cost per test is about US$0.26.	To be determined.
Delivery/ procurement channels	Potentially appropriate for community and small clinic settings, on wards in larger facilities, and demographic surveys. Distribution channels are yet to be determined.	Potentially appropriate for community and small clinic setting, on wards in larger facilities, and demographic surveys.	Distribution to higher-level facilities that require continuous monitoring of hemoglobin and other indicators.	Appropriate for health clinics with power. Procurement exists through standard medical supplies channels.	Appropriate for higher-level facilities with the human resources to run the device and interpret results as well as financial resources and patient volume to justify the cost. Device manufacturers work through in-country distributors to provide up-front sales and ongoing maintenance.	In-country distributors will need to be identified to register and distribute the Claro system and provide maintenance.
Sustainable business models	Biosense is still raising capital investment for continuing development; in effect a social enterprise.	Currently marketing devices in Europe.	Still considered a startup; business sustainability is unknown.	Technology is viewed as a commodity and distributed by multiple suppliers.	Multiple entrants in this technology space indicating that a sustainable business model exists without donor support.	Still being determined.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2					
	TouchHb	**Haemospect®**	**NBM-200MP**	**Hematocrit-centrifuge**	**Hematology analyzer**	**Multiplex anemia etiology tool**
Existing demand	MOH and private-sector clinics without the infrastructure or resources required for a hematology analyzer. The priority market segment are women coming in for antenatal and postnatal services Other users would be community outreach campaigns, nutrition population surveillance, blood donation, and child health programs. Demand drivers are dependent upon the number of community facilities with consistent or intermittent power, frontline health workers with occasional access to electricity conducting anemia screening, or ANC clinics.	MOH and private-sector clinics without the infrastructure or resources required for a hematology analyzer, anemia outreach campaigns, and blood donation. Demand drivers are dependent upon the number of community facilities with consistent or intermittent power, frontline health workers with occasional access to electricity conducting anemia screening, or ANC clinics.	Higher-level facilities that require continuous hemoglobin monitoring. Demand drivers are dependent upon the number of higher-level facilities with consistent power conducting surgery, anemia screening, or ANC clinics.	Public and private health clinics with laboratory technicians and access to electricity or batteries without the infrastructure or resources required for a hematology analyzer. Demand drivers are dependent upon the number of mid- and higher-level facilities with consistent or intermittent power conducting surgery, anemia screening, or ANC clinics.	Public and private hospitals with central laboratories and access to electricity and significant patient volumes. Demand drivers are dependent upon the number of higher-level facilities with consistent power providing inpatient services.	Both the higher-level facility which relies upon smear microscopy for malaria diagnosis and the lower-level clinics which use rapid diagnostic tests for malaria and do not have a hematology analyzer for Hb analysis. Demand drivers are dependent upon the number of community facilities with consistent power conducting anemia screening, malaria screening, or ANC clinics.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2					
	TouchHb	**Haemospect®**	**NBM-200MP**	**Hematocrit-centrifuge**	**Hematology analyzer**	**Multiplex anemia etiology tool**
Attractiveness	Device is simple to use, and noninvasive nature is viewed as a significant advantage. The device still needs to be validated for accuracy and readiness for field use.	Device is relatively simple to use, and noninvasive nature is viewed as a significant advantage. The device still needs to be validated for accuracy and readiness for field use.	Device is simple to use, and noninvasive nature is viewed as a significant advantage. The device still needs to be validated for accuracy and readiness for field use.	Requires no dilution or lysing; results available in 4 to 5 minutes; can run multiple samples concurrently. Barriers include either anticoagulated blood or capillary tubes with anticoagulant must be used. Electricity or battery power is required. Heating of the centrifuge may cause some red blood cell lysis which interferes with the reading. Glass capillary tubes may break when centrifuged. Glass capillary tubes must be disposed of safely. Use of slower centrifuges may result in inaccurate readings.	The gold standard for higher-level facilities; provides accurate complete blood counts necessary to make determination as to the causality of anemia.	Final design specifications are still being worked out. However, the device will likely benefit from providing a wide range of diagnostic indicators, reducing usage of consumables such as buffer, and requiring very little training. Disincentives to use are likely need for internet connectivity, higher up-front costs, and no established supply and maintenance network.
Price sensitivity	Rural clinics are especially price sensitive to recurring costs and anchor to cost of the Sahli method.	Rural clinics are especially price sensitive to recurring costs and anchor to cost of the Sahli method.	Higher-end facilities are less price sensitive but would need to provide value for the money.	Rural clinics are especially price sensitive to recurring costs and anchor to cost of the Sahli method. Additionally, the cost of a technician must be factored in to the true cost of ownership.	Higher-end facilities are less price sensitive but would need to provide value for the money.	Higher-end facilities are less price sensitive but would need to provide value for the money. Rural clinics are especially price sensitive to recurring costs and anchor to cost of the Sahli method.

Demand Information	TECHNOLOGY/SOLUTION—TABLE 2					
	TouchHb	**Haemospect®**	**NBM-200MP**	**Hematocrit-centrifuge**	**Hematology analyzer**	**Multiplex anemia etiology tool**
Policy environment	Biosense was founded by Indian nationals and is based in India where anemia has been identified by the government as a top priority.	Screening is part of the overall integrated strategy for combating maternal anemia. A rapid, accurate, and safer tool will further support these efforts. A noninvasive device has the advantage of not requiring a blood draw, which is a barrier in some settings.	Screening is part of the overall integrated strategy for combating maternal anemia. A rapid, accurate, and safer tool will further support these efforts. A noninvasive device has the advantage of not requiring a blood draw, which is a barrier in some settings.	Well-established and supported method to determine anemia but requires technical expertise and laboratory facilities.	This is a well-established, gold-standard method that is in most central-level facilities and in other facilities equipped with laboratories and skilled technicians.	Determining the cause of anemia is a key element of combating maternal anemia, especially in countries where malarial and parasitic infections are prevalent. A point-of-care tool in resource-poor settings (where automated hemolyzers are scarce) would provide health providers with the information they need.
Donors/ stakeholders	Various donor support and funds from venture capital and Indian investors. Support from the Indian Department of Biotechnology is being sought. PATH is supporting aspects of development and user assessments.	Unknown.	Unknown.	WHO, UNICEF.	WHO, UNICEF.	USAID/HealthTech has supported work on this tool. PATH has engaged with Claro in the development process.
Pre- and post-sales support	Training on the device for proper usage and replacement of probes are required.	Training on the device for proper usage and replacement of probes are required.	Training on the device for proper usage and replacement of probes are required.	Required: initial training; occasional maintenance; and recurring purchase of consumables.	Required: initial training; occasional maintenance; and recurring purchase of consumables.	Required: initial training; occasional maintenance; and recurring purchase of consumables.
Need for demand creation	Yes; noninvasives have a significant advantage over existing screening methods. Further local accuracy and field studies are required to generate demand.	Yes; noninvasives have a significant advantage over existing screening methods. Further local accuracy and field studies are required to generate demand.	Yes, noninvasive have a significant advantage over existing screening methods. Further local accuracy and field studies are required to generate demand.	Efforts to create and build awareness would drive adoption.	No; current gold standard.	Efforts to create and build awareness would drive adoption.

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Treatment of Severe Anemia with Iron Therapy

Severe anemia, defined as hemoglobin less than 7 g/dl, usually comprises a small proportion of the cases of iron-deficiency anemia in a population, but the risk of dying is highest with severe anemia. Therefore, it is important that primary health care providers be able to recognize these cases and treat or refer individuals with severe anemia who do not respond to oral iron therapy or who are at urgent risk of serious complications.[1] Women with severe anemia should be referred for investigation of the cause(s) and for treatment. Treatment should be given in a hospital if the individual is a pregnant woman beyond 36 weeks gestation (i.e., in the last month of pregnancy), or if signs of respiratory distress or cardiac abnormalities (e.g., labored breathing at rest or edema) are present. The different treatment alternatives should be discussed with the patient, taking into account gestational age, cost and availability of the different preparations, and transport possibilities. Pregnant women diagnosed with severe anemia should be treated with 120 mg iron + 400 µg folic acid daily for three months. After completing three months of therapeutic supplementation, pregnant women should continue a preventive supplementation regimen. Those diagnosed with severe anemia and treated with oral iron and folic acid therapy should be asked to return for evaluation of hemoglobin levels one week and four weeks after iron supplementation is begun. The purpose of this follow-up is to refer women who are in need of further medical attention due to low hemoglobin and clinical signs of respiratory and/or cardiac distress. Specifically, women should be referred to a hospital if their condition has worsened by the one-week follow-up visit or if their condition shows no improvement at the four-week follow-up visit.

A Cochrane review found oral, intramuscular (IM), and intravenous (IV) iron to increase maternal hemoglobin values; however, the data were not sufficient to ascertain the clinical significance of these findings.[2] Hence, no treatment for iron-deficiency anemia in pregnant women could be recommended by this review. Oral iron therapy has been shown to be effective in correcting iron-deficiency anemia in most cases and should be considered as the first line of treatment.[3,4] Its effectiveness in programs may, however, be limited in some patients because of the dose-dependent side effects, lack of adherence with taking a medication daily, and insufficient absorption.[5,6] Gastrointestinal side effects (nausea and constipation) were noted to be more frequent with oral iron and did not decrease with controlled-release iron.[7,8,9] In cases in which oral iron has been ineffective or associated with side effects, counseling on adherence and the importance of taking iron-folate daily during pregnancy have often successfully addressed patient concerns. IM and IV iron are treatment options. Maternal hemoglobin at four weeks was higher, and a hemoglobin level of >11 g/dl at birth was more frequent with IV iron as compared with oral iron. Compared with oral iron, hematological parameters were better with IM iron, and compared with IM iron, the parameters were better with IV iron.[2,7,10,11,12] However, the hematologic response to parenteral iron treatment is not faster than the response to oral iron.[13] Mobilization of iron from IM sites is slow and occasionally incomplete.[14] As a result, the rise in the hemoglobin concentration is only slightly faster than that which occurs following the use of oral iron

preparations. Patients who have very brisk, continuing bleeding are difficult to treat with an IM regimen because repeated courses of IM iron are painful, and the utilization of iron given intramuscularly is variable. Patients with severe malabsorption and/or malnutrition may not be candidates for IM treatment if they have a markedly reduced muscle mass into which the iron preparation can be injected. IM injection of iron can produce pain and skin discoloration at the injection site and a variable degree of efficacy.[2] Although no data on toxicity of IV iron use during the first trimester of pregnancy are available, for safety reasons, IV preparations should be considered only after the second trimester. IV iron dextran, iron gluconate, and iron sucrose have been considered for the correction of iron-deficiency anemia during pregnancy, with most data relating to iron sucrose. Because of serious, unpredictable, and life-threatening anaphylactic reactions associated with iron dextran in 0.6 percent to 2.3 percent of patients, and the availability of the two safer IV iron agents, iron dextran is not commonly recommended in practice.[15,16,17,18,19] Consistent data through controlled and randomized trials are available for IV iron sucrose, while only limited published data are available on iron gluconate.[3,10, 20,21]

The following table describes the three most commonly used methods for iron treatment for severe anemia.

Supply Information	TECHNOLOGY/SOLUTION		
	Iron tablets	**Intravenous (IV) iron**	**Iron by injection**
Description	Oral ferrous sulfate tablets are simple, inexpensive, and relatively non-toxic. Iron sulfate is the cheapest preparation. Dosage is variable: some tablets contain 325 mg of iron salts, of which 150–200 mg is elemental iron;[22] and others are 200 mg, of which 60 mg is elemental iron.[23] Gastrointestinal tract symptoms (e.g., abdominal discomfort, nausea/vomiting, diarrhea/constipation) suffered by some patients seem to be directly related to the amount of elemental iron ingested.	Delivered intravenously as a way to replenish hemoglobin (Hb) and depleted iron stores. Given when severe anemia is identified and when oral therapy has failed or oral absorption is seriously compromised and benefit from oral therapy cannot be expected. This form of therapy is more expensive and carries risks. Infusion rate can be metered for monitoring purposes. Comes in various formulations: • Iron dextran (low molecular weight). • Ferumoxytol. • Iron sucrose. • Sodium ferric gluconate.	Injected intramuscularly as a way to replenish Hb and depleted iron stores. Intramuscular (IM) iron injections are given only when severe anemia is identified and when oral therapy has failed or oral absorption is seriously compromised and benefit from oral therapy cannot be expected. This form of therapy is more expensive and carries increased risks. Most common formulation is iron dextran. IM injections are recommended when IV infusions are not an option or side effects from the infusion are not tolerated.
Characteristics applicable for low-resource settings	Multiple manufacturers and in-country suppliers. Thermostable and broad safety profile.	To be considered only when oral iron is unable or unlikely to work. Works better than IM delivery; carries fewer risks but requires trained providers and the necessary set-up and equipment. In comparison with oral iron therapy, treatment with parenteral iron is more complex, more expensive, and can be associated with severe adverse drug reactions. It should be reserved for those with severe intolerance to oral iron or severe anemia is identified and before transfusion is considered. Ferric gluconate and iron sucrose require multiple infusions in contrast to low molecular weight iron dextran, which is in one administration-total dose infusion.	IM injections of iron are considered only when oral iron is unable or unlikely to work and when IV infusions are not an option or not tolerated by the patient. The rise in the Hb concentration is only slightly faster than that which occurs following the use of oral iron preparations. Injection can be painful, and certain formulations such as iron dextran are known to cause adverse reactions and are not recommended for IM use. Requires several steps and special training for delivery technique and monitoring for adverse reactions. For example, needles must be changed between withdrawal of iron from vial and injection to minimize staining of subcutaneous tissues. Location of the injection is critical (always in the upper quadrant of the buttock).
Developer and/or manufacturer	Various manufacturers.	INFeD® (iron dextran) by Sanofi-Aventis (Patheon), distributed by Watson Pharma. Ferrlecit by Sanofi-Aventis, distributed by Watson Pharma.	Jectofer® (iron sorbitol; for IM use only) by Astra Pharmaceuticals. INFeD® (iron dextran) by Sanofi-Aventis (Patheon), distributed by Watson Pharma.
Status	Commercialized.	Commercialized. All forms of IV iron are approved in the United States and Europe.	Commercialized.

Supply Information	TECHNOLOGY/SOLUTION		
	Iron tablets	**Intravenous (IV) iron**	**Iron by injection**
Efficacy/ effectiveness	Highly effective when the patient is adherent and tolerates oral iron.	Effective, but only use if the patient is unable to tolerate oral iron; has a malabsorption syndrome; is considered unreliable to continue oral; is experiencing prolonged erythropoietin therapy (cancer); has a need to rapidly replete iron stores to protect against future bleeding.	Effective for women who cannot tolerate oral iron supplementation and where IV infusions are not an option.
Manufacturing	Multiple suppliers exist for this technology category, suggesting that additional capacity to meet potential demand increases exists within the existing system.	Multiple manufacturers and suppliers exist for this technology category, suggesting that additional capacity to meet potential demand increases exists within the existing system.	INFeD® (iron dextran) by Sanofi-Aventis (Patheon) distributed by Watson Pharma.
Intellectual property ownership	Generic.	As of 2011, the United States did not have any approved generic IV iron products; however, many European, South American, and Asian countries have had numerous so-called iron "similars" introduced into their markets.[24] INFeD®—Watson Pharma.	No generic product is available in the United States for IM iron delivery. INFeD® rights are owned by Sanofi-Aventis.
Cost and cost drivers	Extremely low cost and often provided to patients free of charge. Cost drivers are driven by formulation of iron used. 2001 prices were US$3.00–US$5.11 (1,000 tabs).	Cost of these forms ranges from US$377 to US$688 per gram based on wholesale prices.[25]	Cost: US$377 per gram based on wholesale prices.[25]
Delivery/ procurement channels	Delivery and procurement is through standard in-country medical supply channels. Available through the United Nations Children's Fund (UNICEF) Supply Catalogue.	Delivery and procurement is through standard in-country medical supply channels. National treatment guidelines will need to reflect appropriate use of this product.	Delivery and procurement is through standard in-country medical supply channels.
Sustainable business models	Commodity product with multiple suppliers, suggesting sustainable margins with existing business.	Treatment costs may or may not require donor support and will need to be considered by country within the context of existing financing mechanisms.	Treatment costs may or may not require donor support and will need to be considered by country within the context of existing financing mechanisms.

Demand Information	TECHNOLOGY/SOLUTION		
	Iron tablets	**Intravenous (IV) iron**	**Iron by injection**
Existing demand	World Health Organization (WHO) guidelines and most national country guidelines require use of supplements for all pregnant women. Users will be pregnant and postpartum women with severe anemia. Market size driven by number of pregnant and postpartum women.	Unclear demand for IV iron treatment of severe maternal anemia. This may be due to worry about risks and lack of clear WHO guidelines and recommendations. Users will be pregnant and postpartum women who are severely anemic. Market size driven by number of pregnant and postpartum women with severe anemia and when oral therapy has failed or oral absorption is seriously compromised and benefit from oral therapy cannot be expected.	Unclear demand for intramuscular (IM) iron treatment of severe maternal anemia. This may be due to worry about risks and lack of clear WHO guidelines and recommendations, as well as lack of clear evidence on efficacy. Users will be pregnant and postpartum women who are severely anemic. Market size driven by number of pregnant and postpartum women with severe anemia and when oral therapy has failed or oral absorption is seriously compromised and benefit from oral therapy cannot be expected.
Attractiveness	Effective, low cost, easy to take for most women. Barriers to use are availability at the last mile, and side effects, which reduce adherence.	Better option than blood transfusions. IV iron delivery is more common than IM. Preferred parenteral delivery mode. Expensive and requires IV equipment and trained medical staff.	More available at peripheral facilities where administration of IV drugs is not possible. Perceived as less risky than IV infusions. Requires injection and trained medical staff.
Price sensitivity	Procured by the public sector for free distribution. Often, lowest-cost product is chosen over side-effect profile.	Will be used only when oral supplementation is not an option.	Will be used only when oral supplementation or IV delivery is not an option.
Policy environment	Oral iron is the most widely recommended approach to the treatment of severe anemia, where and when possible and appropriate. Policy environments are very supportive of this approach.	WHO is unable to clarify treatment recommendations for prenatal and postnatal anemia due to lack of large, high-quality clinical trials assessing treatment outcomes[26] and concerns about possible adverse effects.	WHO is unable to clarify treatment recommendations for prenatal and postnatal anemia due to lack of large, high-quality clinical trials assessing treatment outcomes[26] and concerns about possible adverse effects.
Donors/ stakeholders	WHO, UNICEF, the Global Alliance for Improved Nutrition, and the United States Agency for International Development are supportive of this line of treatment.	Donor and stakeholder views on this intervention are unclear.	Donor and stakeholder views on this intervention are unclear.
Pre- and post-sales support	Needs a consistent last-mile supply chain.	Training on safe delivery, procurement, and rational use will need to be implemented in most countries.	Training on safe delivery, procurement, and rational use will need to be implemented in most countries.
Need for demand creation	Need to generate awareness among patients with regard to the risk of anemia and benefits of supplementation.	Medical societies in each country will need to consider the role of IV iron for the treatment of anemia in their national guidelines.	Medical societies in each country will need to consider the role of IM iron for the treatment of anemia in their national guidelines.

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