

The Sino-implant (II) Initiative: Expanded Access to Contraceptive Implants

Contraceptive implants, introduced more than 30 years ago, are one of the most effective family planning methods available. They are ideal for women with limited access to health care services because they are long-acting methods that do not require regular resupply from a provider. Yet, until recently, access to implants in resource-constrained countries has been limited, largely because of their cost.

Catalyst for Lower Costs

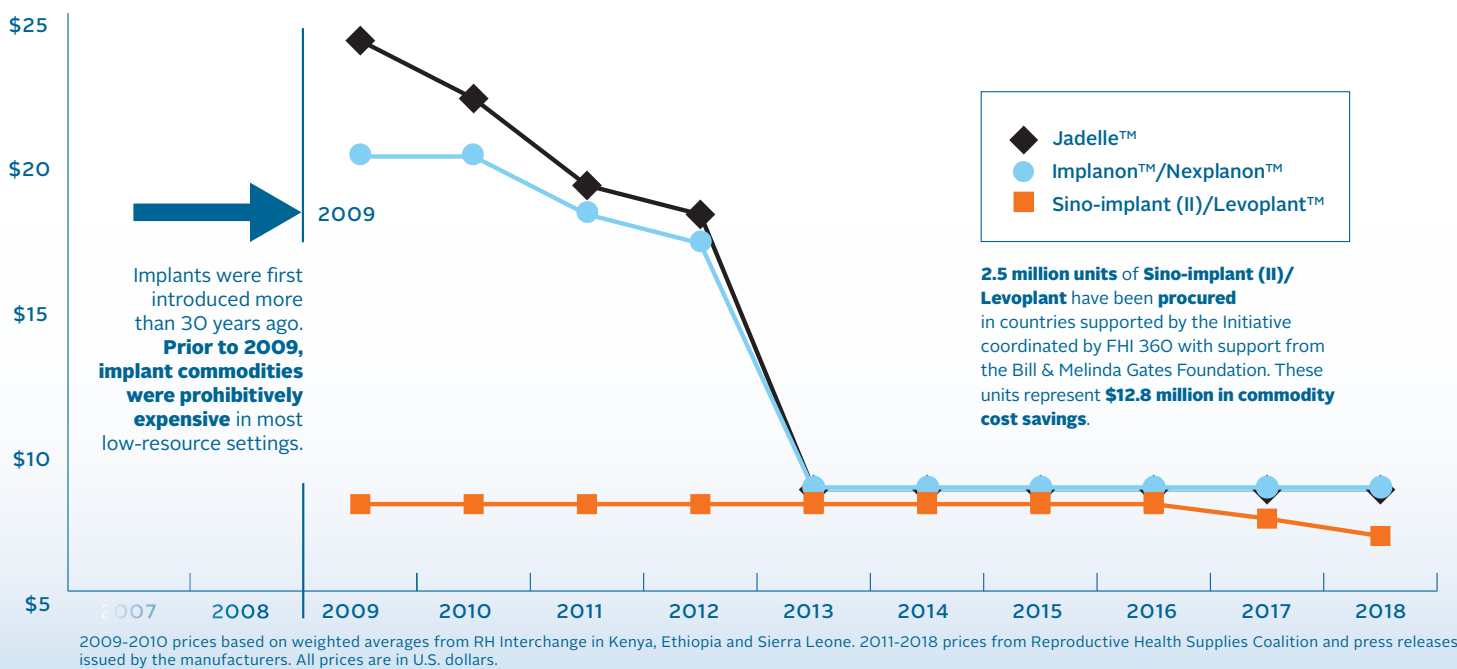
For the past decade, the FHI 360-led Sino-implant (II) Initiative has been at the forefront of improving access to high-quality, affordable contraceptive implants. By expanding access to a relatively low-cost implant — Sino-implant (II) — the Initiative helped increase competition and reduce costs in the implant market (see Figure 1).

The Product

Sino-implant (II) consists of two thin rods that are inserted into a woman's upper arm, where they slowly and continuously release the hormone levonorgestrel (LNG). Manufactured by Shanghai Dahua Pharmaceutical Co., Ltd. (Dahua), Sino-implant (II) was prequalified by the World Health Organization (WHO) in June 2017.¹ The WHO-prequalified contraceptive implant is now being distributed globally by DKT WomanCare as Levoplant.TM



Figure 1. Contraceptive Implant Prices, 2009-2018: Changes since global introduction of Sino-implant (II)/Levoplant



2009: Sino-implant (II) registered in Kenya under trade name Zarin; first registration outside of Asia

2011-2012: Merck/MSD reduces price of Implanon to \$18/unit, with retroactive reduction to \$16.50 when volume thresholds reached

Bayer HealthCare reduces price of Jadelle to \$19/unit and subsequently to \$18/unit

2012-2013: Bayer HealthCare and Merck/MSD lower the prices of Jadelle and Implanon to \$8.50 per unit as part of volume guarantees in FP2020 countries

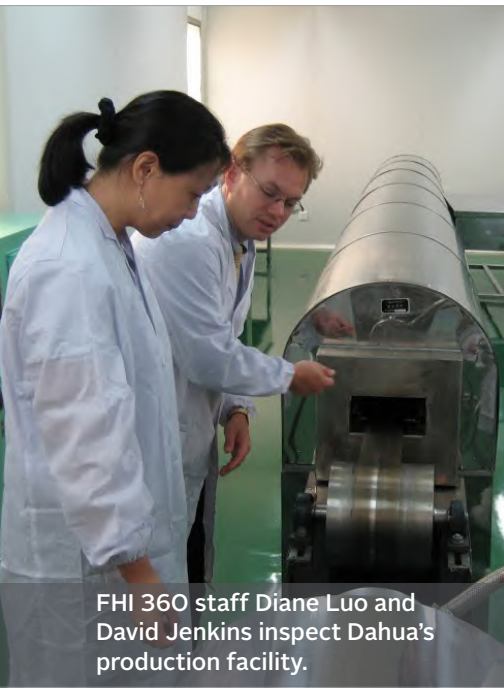
2017: Levoplant prequalified by the World Health Organization

2018: Dahua forms partnership with DKT International to act as global distributor and announces price reduction of WHO-prequalified Levoplant to \$6.90 in FP2020 countries

KEY MILESTONES

FHI 360's Role

Under the Sino-implant (II) Initiative, funded by the Bill & Melinda Gates Foundation, FHI 360:



FHI 360 staff Diane Luo and David Jenkins inspect Dahua's production facility.

- Supported Dahua's application for WHO prequalification, including conducting clinical trials, compiling the product dossiers and facilitating Good Manufacturing Practice (GMP) inspections
- Developed a disposable trocar to reduce infection risk, including HIV transmission, and facilitate service delivery
- Conducted annual independent quality assessments of Sino-implant (II)
- Negotiated public-sector price-ceiling agreements with distributors
- Spearheaded national regulatory approvals
- Evaluated safety, effectiveness and acceptability in surveillance studies
- Designed the product packaging and drafted the text of product information for clients and providers
- Negotiated procurement contracts to access the global supply chain
- Developed training materials, represented Dahua at global stakeholder meetings, and provided technical assistance to countries for product introduction
- Collaborated with the Clinton Health Access Initiative (CHAI) to identify a global distribution partner, DKT WomanCare, to work with Dahua at the end of FHI 360's involvement with the product.

More information about each of these activities is provided below.



Dahua's General Manager Guoqiang Zhang and FHI 360 staff Diane Luo and Markus Steiner meet with Bill Gates in Beijing in May 2012.

WHO prequalification

WHO prequalified Sino-implant (II)/Levoplant on June 30, 2017,¹ after reviewing the product dossier, including new clinical trial data from the Dominican Republic² and China,³ and inspecting Dahua's manufacturing facility to ensure that it complied with WHO GMP. WHO prequalification is necessary for international procurement agencies, such as UNFPA and USAID, to distribute a product, and it facilitates registration at the country level. Levoplant is WHO-prequalified for a three-year duration of use.

FHI 360's support for Dahua's prequalification application included conducting clinical trials in the Dominican Republic and China to evaluate the product's safety, effectiveness and acceptability; submitting the dossier

and responding to technical queries on behalf of Dahua; improving manufacturing processes, including developing testing methods that met WHO requirements; and facilitating GMP inspections of the Dahua facility in Shanghai, China.

Disposable trocar

Prior to this Initiative, stainless steel trocars requiring sterilization were used for both Sino-implant (II) and Jadelle™ insertions. In low-resource settings, where many family planning clinics did not have working autoclaves, clinics either could not offer implants or would reuse instruments without adequate sterilization. Suboptimally sterilized trocars can spread HIV and other blood-borne disease. To solve this problem, FHI 360 was the first to develop a disposable trocar for a two-rod contraceptive implant. We also conducted a study in Kenya⁴ to obtain a CE Mark for the disposable trocar. A certification for the distribution of medical devices in Europe, the CE Mark is increasingly required by regulatory bodies across Africa, Asia and Latin America, as well as global procurers.

Quality testing

Annual quality testing of Sino-implant (II), conducted by FHI 360 beginning in 2008, complemented Dahua's ongoing lot-release testing.⁵ In these tests, Dahua demonstrated the ability to consistently produce a contraceptive implant that meets international quality standards. In addition, FHI 360 assessed product

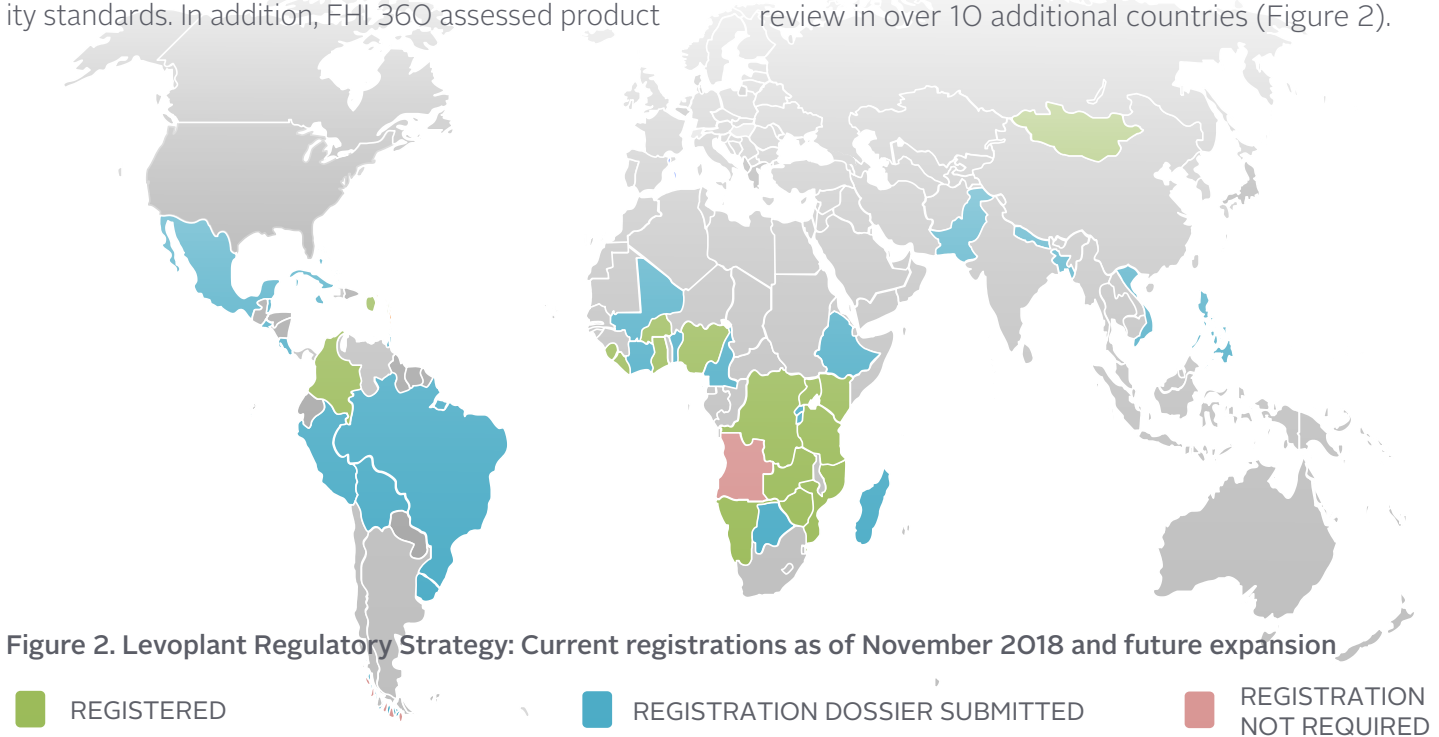
quality by measuring the LNG remaining in Sino-implant (II) used for up to seven years and compared results with published data for Jadelle explants used for up to 36 months. Both products release approximately 30 percent of total LNG load after three years with similar estimated daily release rates.⁶

Pricing agreements

FHI 360 negotiated price-ceiling agreements with distributors to ensure that Sino-implant (II) remained affordable in the public and nonprofit sectors.

National regulatory approvals

Leading up to WHO prequalification, FHI 360 worked with a variety of partners to establish a global regulatory footprint and distribution platform. Through these efforts, we supported registration of Sino-implant (II) by over two dozen drug regulatory authorities worldwide. Starting in July 2017, FHI 360 began to update these registrations for the new WHO-prequalified product globally branded Levoplant. At the end of the Sino-implant (II) Initiative in November 2018, Levoplant had been registered in 15 countries, and dossiers were under review in over 10 additional countries (Figure 2).



Burkina Faso, Colombia,* DRC, Ghana, Kenya, Liberia, Malawi, Mongolia, Mozambique, Namibia, Nigeria, Myanmar,* Sierra Leone, Tanzania, Uganda, Zambia, Zimbabwe, Regional approval through CARICOM*± (Barbados, Belize, Dominica, Guyana, Haiti)

Bangladesh, Botswana, Brazil, Benin, Burundi, Bolivia, Cameroon, Côte d'Ivoire, Costa Rica, Ethiopia, Guatemala, Madagascar, Mali, Mexico, Nepal, Peru, Pakistan, Philippines, Rwanda, Vietnam

Angola

* 4-year non-PQ

± still requires local importer to be appointed for national approval

Surveillance studies

Chinese clinical data from the early 1990s from four randomized trials among over 15,000 women had shown that Sino-implant (II) was highly effective, with annual pregnancy rates below 1 percent.⁷ With funding from the Gates Foundation and USAID, FHI 360 and partners conducted surveillance studies with cohorts of women using the product in Bangladesh, Kenya, Madagascar and Pakistan and followed them for the first year of use. The results showed that Sino-implant (II) is a safe, highly effective method. In Bangladesh and Madagascar, no post-insertion pregnancies were reported; in Kenya and Pakistan, the combined annual pregnancy rate was below 1 percent.⁸⁻¹⁰

Packaging and client/provider information

FHI 360 drafted and worked with WHO to finalize the product packaging and the information about the product provided to clients and providers, respectively, in the Product Information Leaflet (PIL) and Summary of Product Characteristics (SmPC).



Global procurement contracts

FHI 360 negotiated procurement contracts for contraceptive products on behalf of Dahua with the two main global procurement agencies, the United Nations Population Fund (UNFPA) and the U. S. Agency for International Development (USAID).

Product introduction and scale-up

FHI 360 developed training materials, represented Dahua at global stakeholder meetings, and provided technical assistance to governments and service delivery groups introducing Sino-implant (II). Information about training, clinical guidelines and other service delivery considerations can be found in the Knowledge for Health Implants Toolkit: <http://k4health.org/toolkits/implants>.

Global distribution partnership

During the last year of the Sino-implant (II) Initiative, FHI 360 collaborated with CHAI to identify potential global distribution partners for Dahua. To achieve a sustainable business model, Dahua formed a partnership with DKT WomanCare and announced a further price reduction to \$6.90 per unit for Levoplant in Family Planning 2020 (FP2020) countries.



How to Insert Levoplant®

FIGURE 1:

- 1 Explain the procedure to the client and encourage questions.
- 2 Determine the required needs for high level disinfection instruments and supplies are present.
- 3 Wash hands and thoroughly dry them.
- 4 Check to see that the implant has thoroughly washed and rinsed for seven min.
- 5 Position the woman's arm and place a clean, dry cloth against her arm.
- 6 Make palpation on arm for insertion of scale 8 cm to 8 cm about the elbow (skin should form a "V" pattern).
- 7 Put on a sterile pair of hand gloves.

FIGURE 2:

- 1 Cut a sterile, full and place implant ends and prick on it.
- 2 Prep insertion site with antiseptic solution.
- 3 Place depth of high level disinfection cap on arm.
- 4 Inject 2 ml of local anesthetic applied just under the skin, using a wheel of the insertion point and advancing up to 1 cm along the top reaction track, injecting 1 ml of local anesthetic along track to second reaction track, injecting 1 ml of local anesthetic along track to third reaction track, injecting 1 ml of local anesthetic along track to fourth reaction track. Let the arm rest for approximately 10 minutes and check for anesthetic effect before making skin incision.

FIGURE 3:

- 1 Make a small incision with a scalpel in the skin on the inside of the upper arm. Alternatively, use the trocar to puncture the skin. Insert the tip of the trocar against the skin at a shallow angle. Gently advance the trocar gradually under the skin until the head of the trocar is just under the skin. Support the skin while the implant is placed under the skin and not directly into the arm. Do not spread the skin. Support the skin. The great care not to insert trocar into the arm directly. The Sino-implant has been used in the past. The mark on the top of the implant should be placed in the skin. The mark on the top of the implant should be placed in the skin. The mark on the top of the implant should be placed in the skin.

FIGURE 4:

- 1 When the trocar has been inserted to the mark closest to the skin, remove the obturator and hold the top of the implant into the tissue using the "V" and handgrip.

FIGURE 5:

- 1 Using the obturator to push, gently advance the implant towards the tip of the trocar until you feel resistance. Now remove the obturator.

FIGURE 6:

- 1 Holding the obturator stationary, withdraw the trocar in the same direction as you inserted it. The implant should be released under the skin at this point. It is important to keep the obturator stationary and to avoid pulling the implant into the tissue. Do not completely remove the trocar until both implants have been placed.

FIGURE 7:

- 1 To place the second implant, align the trocar so that the second implant will be positioned at about a 30° angle relative to the first implant. Repeat steps 2-6. The rods are placed in the hollow of a "V" pattern between the incision and the tip of the obturator. Remove the trocar and immediately dispose of it in a sharps container.

FIGURE 8:

- 1 Remove the cap and wipe the client's skin with alcohol.
- 2 Check status of incision together and close a simple suture if there is any gap. Then cover it with tape or a sterile gauze (2x2) or an adhesive bandage.
- 3 Apply pressure, getting strongly.
- 4 Repeat clean regarding wound care.
- 5 Keep the area around the insertion site dry and clean for at least 48 hours.
- 6 Leave the wound pressure bandage in place for 48 hours and the longest length of time possible (up to 72 hours) after the insertion of the implant (usually 3-5 days).
- 7 Discuss with the client what to do if she experiences any problems including irritation or an infection from the product. Advise client that she can have the rods removed at any time if she desires.
- 8 Make a full visit appointment, if necessary.
- 9 Optimize the client for at least 10-20 minutes before departing.

Strategic Impact

Cost savings

A total of 2.5 million units of Sino-implant (II) have been procured in countries included in the Initiative. The WHO prequalification of Levoplant and subsequent partnership with DKT WomanCare have resulted in a dramatic increase in sales, with over 1 million units procured in 2018 alone (Figure 3). Compared with the cost of purchasing other types of implants during this time, these procurements represent a commodity savings of \$12.8 million for service delivery groups and donors.¹¹

Public health impact

The use of the 2.5 million Sino-Implant (II) units procured under the Initiative will avert an estimated:

- 3.3 million unintended pregnancies
- almost 9,000 maternal deaths
- 1.3 million abortions

based on estimates generated by Marie Stopes International's Impact 2 calculator.¹²

Moreover, the public health impact of the use of 2.5 million implants translates into \$143 million total health care costs saved.

More affordable implants

Before the Sino-implant (II) Initiative began, the cost of Sino-implant (II) was about one-third that of other implants on the market. In 2010, Jadelle,

a two-rod implant made by Bayer HealthCare, was available at an average price of \$22 for international procurement groups; Implanon™, a one-rod implant made by Merck, was available for \$20.

Bayer lowered the price of Jadelle to \$8.50 per unit in low-income countries starting in January 2013 as part of a volume guarantee agreement brokered by a coalition of international partners.¹³ A year after reducing the price of Implanon to \$16.50 in 2012, Merck announced another 50 percent unit price reduction to \$8.50 in developing countries. By 2013, Jadelle and Implanon/Nexplanon™ were available at a price comparable to that of Sino-implant (II).

Expanded access to implants

The reductions in implant prices spurred by competition and subsequent market shaping interventions — along with greater commitment by governments and donors to expand access to long-acting methods and changes in policies and service delivery practices — have led to increases in contraceptive prevalence and expansion of countries' method mix. In the past few years, use of implants in sub-Saharan Africa has increased dramatically (see Figure 4). A study of 12 African countries for which comparable data were available found that implants drove recent increases in contraceptive prevalence in 11 countries. Implants are now the first or second most widely used contraceptive method in 10 African countries.¹³

Figure 3. Dahua Sales of Sino-Implant (II)/Levoplant, 2008-2018*

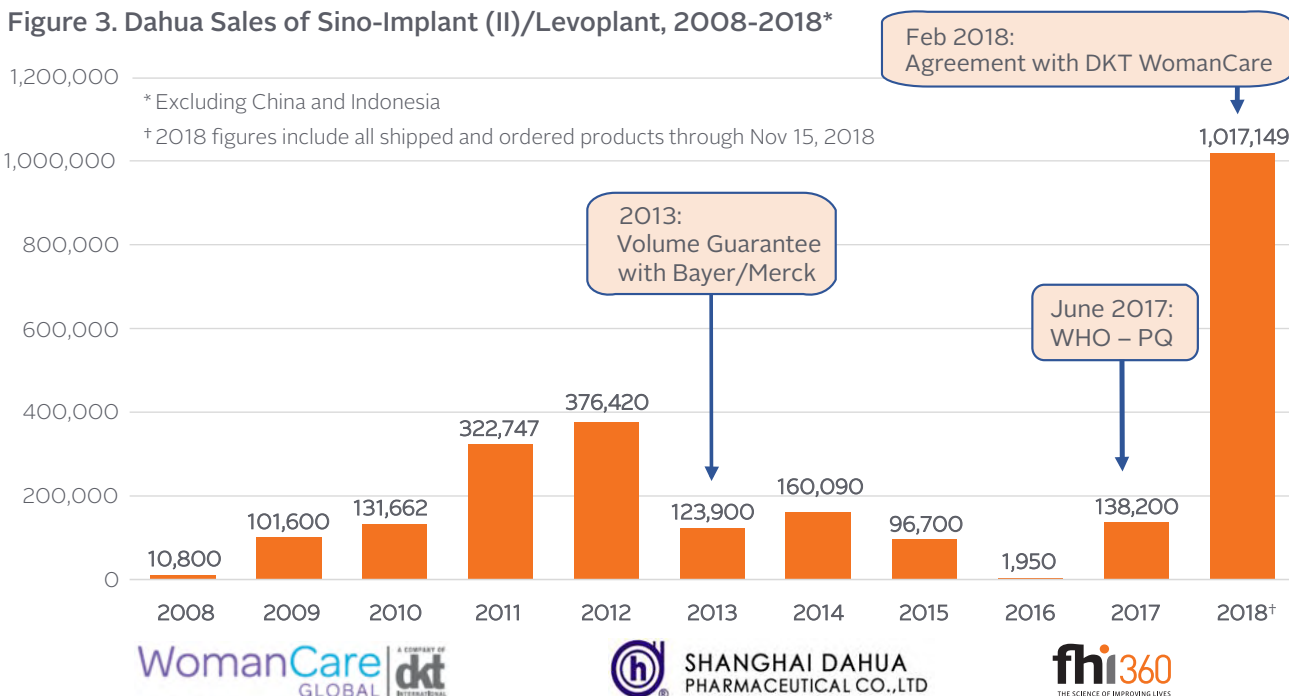
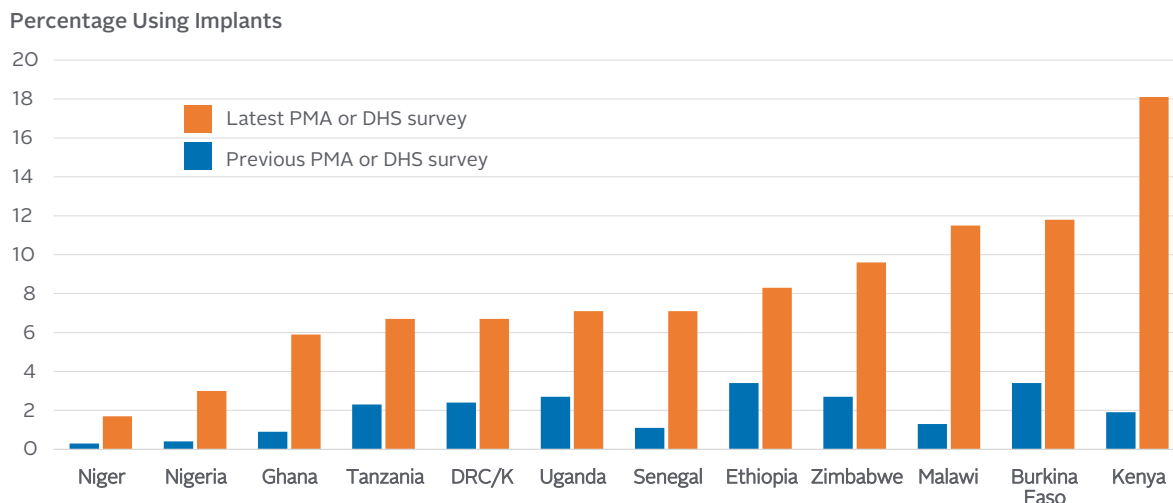


Figure 4. Marked Increases in Implant Use by Married Women, 2008–14 to 2015–17¹³



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