ISSUE BRIEF

MÉDECINS SANS FRONTIÈRES ACCESS CAMPAIGN

A CENTURY OF NEGLECT: CHALLENGES OF ACCESS TO INSULIN FOR DIABETES CARE

INTRODUCTION

An estimated 422 million people are living with diabetes worldwide.[1] Prevalence has nearly doubled over the past 30 years and is now rising faster in low- and middle-income countries than in high-income countries.[1]

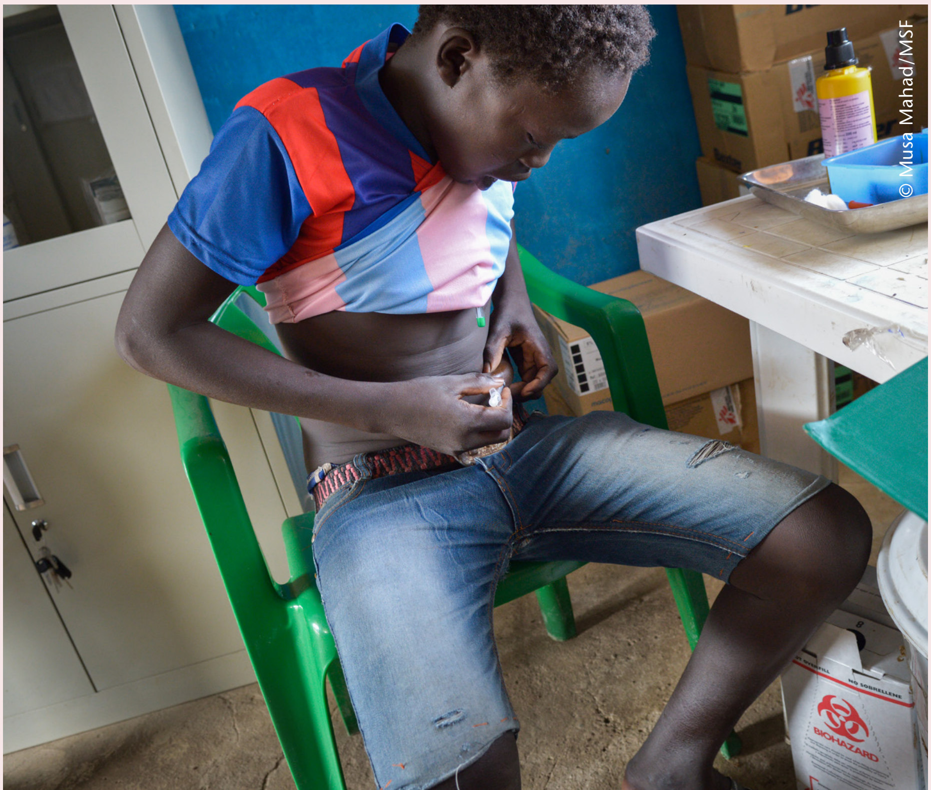
Diabetes is a chronic, progressive disease that can be controlled with effective treatment. However, in many countries, people living with diabetes are not getting the treatment they need to stay healthy. In fact, only about half of people requiring insulin have access to it.[2]

The two major types of diabetes are type 1 and type 2. In type 1 diabetes (T1D), a disease that presents in children, adolescents and young adults, an absolute lack of insulin production by their pancreas means that within a few days or weeks without insulin treatment, they will die. Globally an estimated 1.1 million children and adolescents under the age of 20 are living with T1D. The total number of people living with T1D is estimated at 20 million, but data from many low-income settings are sparse.[3] To treat T1D, a number of medicines and diagnostic tools are needed, including insulin itself, the delivery device to inject it and a means of monitoring blood glucose on a daily basis. Treatment requires multiple daily injections and in most cases multiple checks of blood glucose using invasive finger-prick sampling.

In type 2 diabetes (T2D), the body either does not produce enough insulin or becomes resistant to it. T2D accounts for the majority of people living with diabetes worldwide.

An estimated 10-15% of people living with T2D will also need insulin. Without adequate control of blood sugar in either type of diabetes, acute life-threatening crises can occur, as well as serious long-term complications including kidney failure, blindness, heart attack, stroke or limb amputation.

MSF works in over 70 countries worldwide and in most of these settings, insulin is often not available in public health facilities or private pharmacies.[4] In 20 projects across 11 countries, MSF focuses on diabetes as one of the most common non-communicable diseases (NCDs) in people receiving care in our clinics. In 2018, MSF provided insulin for 1,142 people with T1D and 4,038 people (of 14,824 total) with T2D. The majority (84%) of people receiving diabetes care from MSF are in Jordan, Lebanon and Iraq, including refugees fleeing the humanitarian crisis in Syria. Projects providing care for T1D in sub-Saharan African settings such as South Sudan, Democratic Republic of Congo and Tanzania have been set up in response to patients presenting in acute crisis, known as diabetic ketoacidosis (DKA), due to lack of insulin treatment.



Deng Gwin, 14, administering his own insulin injection in MSF's diabetes clinic in Agok hospital, South Sudan, June 2016.

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BARRIERS TO TREATMENT: COST AND COMPLEXITY

So why is insulin, discovered almost 100 years ago (1921), not readily available to people who need it? A combination of factors, including high prices, challenging storage requirements and complex treatment protocols, all contribute to preventing access.

TREATMENT NEEDS TO BE MORE AFFORDABLE

Current data on the cost of insulin production demonstrate the potential for much lower prices than those currently charged by the major insulin manufacturers. The costs to produce a 10mL (1000 units) vial of human and long-acting analogue insulin are US$3.35 and US$5.32, respectively.[5] This equates to US$72 and US$133 per person per year.

The reality of commercial insulin pricing is very different, however. Prices vary significantly among countries and health sectors and are often not publicly known; corporate pricing practices are opaque and difficult to understand. A study performed by the Addressing the Challenges and Constraints of Insulin Sources and Supply (ACCISS) group demonstrated the median government procurement prices of different types of human and analogue insulin in vials were between US$6 and US$34.[4] The median global price for what an individual paid per vial of human insulin was around US$7.50; for a person using 40 units a day, their insulin alone would cost about US$110 per year.

Finally, insulin pens (US$27; see page 4) and cartridges (US$18) are comparatively much more expensive than insulin in vials (Table 1).[6]

TABLE 1. INSULIN PRICES

Insulin product	Price per person per year, US$*[2]
Human vial (10mL)	$110
Human cartridge (3mL)	$876
Analogue vial (10mL)	$496

*Examples of insulin-only price per person per year (using 40 units per day)

In MSF projects, prices of human insulin range from US$2.30 to US$12.15 per 10mL vial. In NCD programmes, insulin ranks in the top five most expensive medicines and has been an issue in considering the number of people MSF is able to treat.

The availability and affordability of insulin is only one piece of the treatment puzzle. Insulin requires a means of delivery (currently only possible through injection or infusion) and a way to monitor its safety and effectiveness. Hence, people also need a package of devices. In MSF projects in the Middle East, the syringes and needles used to inject insulin cost about US$5 per month, in addition to the glucose monitoring strips which can cost US$24-48 per month, depending on local protocols. Therefore the estimate for the package of consumables required to treat a person with T1D is at a minimum $458 per person per year.

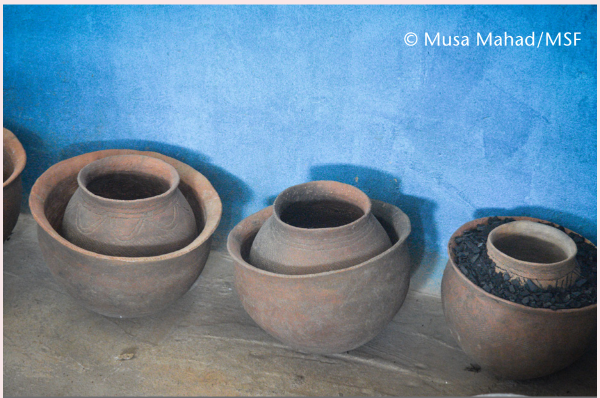
INSULIN STORAGE CAN BE SIMPLIFIED

Storage recommendations for human insulin are below 25°C for 42 days before or after first use. Analogue insulin can be stored for similar periods at a temperature below 30°C.[7] Refrigeration is required for storage of all products until their expiry date.

In many settings where MSF works, room temperatures commonly exceed these temperatures, and people rarely have access to refrigeration at home. The belief that insulin cannot be stored outside of refrigeration has been a barrier to rational insulin prescribing and decentralisation of care.

MSF staff Gifty Vundru, Agok, South Sudan:

"For a long time we have thought that we cannot send our patients home with insulin. This was a massive challenge for our patients. Some of them were travelling 4-5 km a day to get their insulin injections at the clinic. Their whole day was consumed with this. Life is difficult enough without this burden. Now we know that the insulins we have can be stored like this without refrigeration – that is one obstacle we can overcome. Knowing this, we have now developed a patient education programme to enable patients in our programme to inject themselves at home."



Clay pots with a layer of charcoal between them help keep insulin at around 27°C, in Agok, South Sudan, June 2016. These pots enable people to keep a month's supply of medication at home without refrigeration.

In many settings, this results in people being asked to travel to the health clinic for injections and monitoring, at least twice a day, for life.

MSF carried out studies demonstrating that human insulin subjected to temperatures that fluctuate over a 12-hour cycle – with a mean temperature of 31°C – remains stable for up to 12 weeks.[8] Consequently, people can store their insulin in locally made cooling devices at home, and administer their own doses.[9] These simple, improvised methods of cooling have enabled health workers to more confidently set up home insulin programmes allowing people to store a month's supply of insulin.

However, because of product labelling, the need for refrigeration is often cited as a reason not to administer insulin at home. We call for companies to share what further thermostability data they have both for supply and use, and for a consensus statement endorsed by WHO to support the use of locally produced cooling devices for the storage of insulin in order to dispel the notion that refrigeration is needed in every situation.

HOW CAN WE IMPROVE QUALITY OF CARE?

Different levels of care are being provided for people with T1D,[10] starting with twice-daily regimens of human insulin with no home monitoring, progressing to multiple daily injections (MDI) with home blood glucose monitoring—which enables health workers and patients to more accurately adjust doses—and finally, to analogue insulins and pumps. However, these more complex regimens are generally only available in high-income settings.

Using insulin in humanitarian and resource-poor settings remains challenging. Health workers who are not specialists need to be familiar with how to start and titrate insulin, educate patients to self-inject, monitor blood glucose and ideally adjust the dose of insulin themselves. Simplification of protocols and providing expert decision support have been key in establishing programmes using insulin in resource-limited settings.

Apart from a handful of people in the Middle East who are on MDI regimens, a twice-daily regimen of human neutral protamine Hagedorn (NPH) or 30/70 mixed insulin is most often used in MSF projects. Outcomes are variable. A blood test, HbA1C, measures how well the blood glucose has been controlled over the last three months. HbA1C targets should ideally be individualised, but to avoid severe complications, a measurement of 7-8% would generally be considered ideal. In MSF programmes in Lebanon, 30% of people with T1D and 60% of people with T2D had an HbA1C of less than 8%. Programmes in refugee settings in Kenya that have significantly invested in patient education to provide home insulin have reduced episodes of diabetic ketoacidosis, but even so, only 6% of people have an HbA1C of less than 8%. With these poor levels of control, people continue to be at risk of severe early complications such as blindness, amputation and renal failure.

In addition to increasing the complexity of injection and monitoring regimens, health workers cite fear of hypoglycaemia as the key reason for not wanting to increase the doses of insulin to aim for better control. In particular, in many of the humanitarian and low-income settings where MSF works, the issue of food insecurity poses a specific challenge in the management of diabetes and raises additional challenges for dosing of insulin and avoidance of hypoglycaemia.

LIMITED MARKET COMPETITION KEEPS INSULIN PRICES HIGH

MONOPOLY FOR A FEW

Unfathomably, after 100 years, just three multinational corporations (Eli Lilly, Novo Nordisk and Sanofi) continue to dominate the insulin market, controlling 99% by value, 96% by volume and 88% by product registrations. These manufacturers are able to keep prices artificially high, which severely limits access to insulin across the globe. In some countries, prices have actually been increasing significantly, which has contributed to the growing global outrage at exorbitant medicine prices.

Insulin is a biologic medicine (large molecule) and creating "copies" is a more complicated process than producing generic medicines, such as aspirin, that are non-biologic (small molecule). Today approximately 40 companies[11] worldwide produce generic copies of insulin, known as biosimilar insulins, with about 10 companies having significant production capacity—albeit primarily for local markets. Despite this, only glargine (the first long-acting analogue insulin to go off patent) and lispro have biosimilar alternatives approved by recognised regulatory authorities.

To date, no human biosimilar insulins have been approved by such regulators, thus limiting their procurement by MSF, UN agencies and others.

For many generic medicine manufacturers, the WHO prequalification (PQ) programme has been an important route for expedited registration in low- and middle-income countries. In response to the critical need to increase access to insulin, WHO launched a pilot process for insulin prequalification in November 2019.

The introduction of biosimilars should result in lower prices for insulin, although on average the introduction of biosimilars for other diseases such as cancer has resulted in a less significant price drop than the introduction of generic medicines — about 40% for biosimilars compared to more than 90% for generics. The cost-of-production data for insulin cited earlier in this report provide a strong rationale for prices to come down for both human and analogue biosimilar insulin.

AS TECHNOLOGIES ADVANCE, THEY MUST BE MADE ACCESSIBLE

INSULIN PENS

For people living with diabetes in high-income settings, including the Middle East, the norm for insulin delivery is a pen device. Such pens ensure the correct depth of injection and simpler dosing. The dose dial is set by the health worker—or adjusted by the patient if self-adjusting. Insulin pens are much easier to use but remain far too expensive for most people in developing countries.

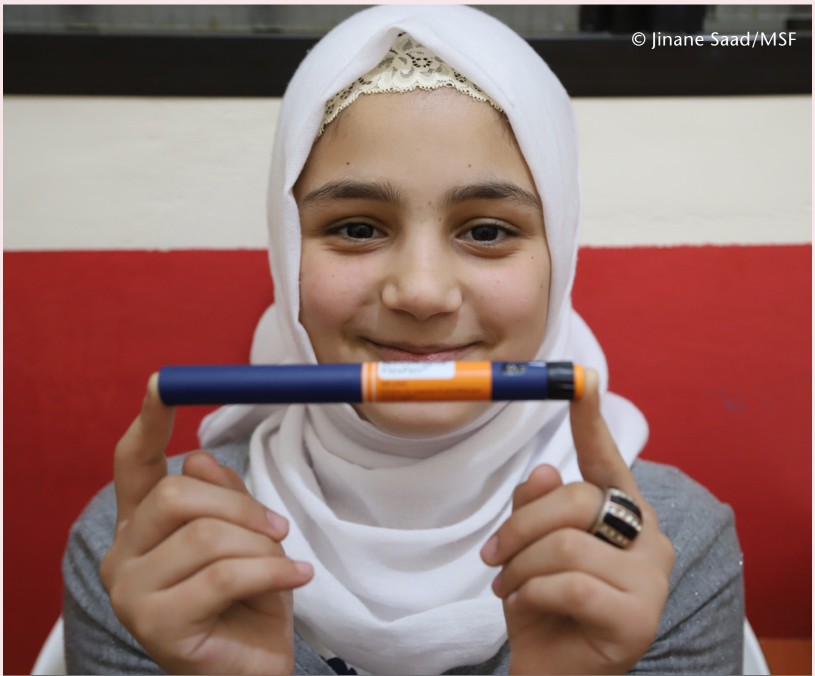
Insulin pens have recently been introduced for children in some MSF projects in the Middle East, but pens have not universally been used in MSF settings due to their high price. Most people in developing countries are using human insulin packaged in a vial and must purchase insulin syringes and needles separately; this is currently the most affordable form of treatment.

Although studies in trial settings have not shown significant differences in HbA1C outcomes between human insulin delivered via pens versus needles and syringes,[12] these studies have not included qualitative research or considered the complications of delivering insulin in challenging humanitarian settings such as refugee camps or remote traditional homes with little light. To administer a carefully measured dose from a vial, a separate syringe and needle are required. Filling the syringe accurately can be difficult for many people, especially for people with visual impairment or lacking numeracy skills. Administering injections to an infant or child is difficult, from managing the pain of the injection to ensuring the correct depth of the needle.

Waste management also needs to be taken into consideration. A twice-daily regimen of human insulin in a vial generates 60 needles and plastic syringes needing disposal each month. Many people in low-resource settings economise by reusing syringes and needles, which can become blunt and painful and potentially pose infection risks. Many pens currently available in MSF are considered "disposable", with each person using up to eight plastic pens every month. Reusable insulin pens that can be used with insulin cartridges may reduce waste and if made from a biodegradable material would reduce the environmental impact of treating diabetes, especially in settings where there may be limited options for waste management.

Dr Lydia Liodaki, MSF doctor, Greece:

"The migrants we were treating on the Greek islands arrived already on insulin and had been using insulin pens for years. We tried to switch them back to vials of insulin using needles and syringes, but they refused as they found it more painful and complicated. It was too difficult and in their stressed circumstances and the short time we had to see them, it became impossible. Also for storage and giving them supplies to carry, it was much easier with the volume of pens rather than all the syringes and needles we were trying to give."



Sidra, a 12-year old girl affected by type 1 diabetes holding an insulin pen at MSF's Shatila Camp, Lebanon, September 2019.

ANALOGUE INSULIN

Analogue insulin is a subgroup of human insulin, genetically altered to change the onset and duration of its action. The first analogue insulin was developed in 1996,[13] but the appropriate use of analogue insulins for T1D is still under debate.

WHO guidance now recommends that long-acting analogue insulins be considered for adults with T1D or T2D who have frequent severe hypoglycaemia with human insulin.[14] For governments to be able to procure analogue insulin more easily, it should be added to the WHO Essential Medicines List (EML). To date, two attempts to do so have been rejected by the EML expert committee. While analogue insulin does have a better safety profile regarding hypoglycaemia, opponents have argued there is not enough evidence to show analogues lead to improved HbA1C outcomes and that their small advantages do not justify their exorbitant prices.

Beyond the quantitative evidence on efficacy and safety, what is also lacking in the debate is the voice of people living with T1D and consideration of qualitative evidence. Impacts on quality of life should be taken into account by the EML expert committee, who have signalled they are open to considering the role of analogue insulins, especially for the treatment of children. In addition, price concerns should not prevent important medicines from being added to the EML. Instead, efforts should be made to reduce the prices of medicines considered critical enough to be listed as essential.

PROPERTIES OF HUMAN AND ANALOGUE INSULINS

Synthetic human insulin	Analogue insulin
Produced by recombinant DNA technology and identical to endogenously produced insulin protein in humans	Subgroup of human insulin, genetically altered in the laboratory to control onset and duration of action
On the WHO Essential Medicines List	Not currently on the WHO Essential Medicines List
Currently least expensive form of insulin	Significantly more expensive
Cost of production: US$3.35 per 10mL vial (1000 units)	Cost of production: US$5.32 per 10mL vial (1000 units)
Must be stored at <25°C after first use	Must be stored <30°C after first use
	Preferred if frequent hypoglycaemia
	Onset of action of short-acting analogues provides more flexibility for timing of meals

GLUCOSE MONITORING

Glucose testing strips are used with monitoring devices for diagnosing diabetes and checking blood sugar levels in people living with diabetes. Strips are single use, not interchangeable between different devices and relatively expensive considering people need to use multiple (sometimes up to eight) strips per day.

Between 2016 and 2017, MSF's total consumption of strips increased by approximately 11% and cost the organisation a relatively large sum — about US$830,000 (€750,000). The cost per strip remained constant at about US$0.22 (€0.20) despite this increase in volume.

In MSF projects in the Middle East, people taking insulin are advised to monitor their blood sugar four to six times per day. They are asked to document their results for health workers to help them assess their control at the next clinical visit, and to guide the adjustment of their insulin dose.

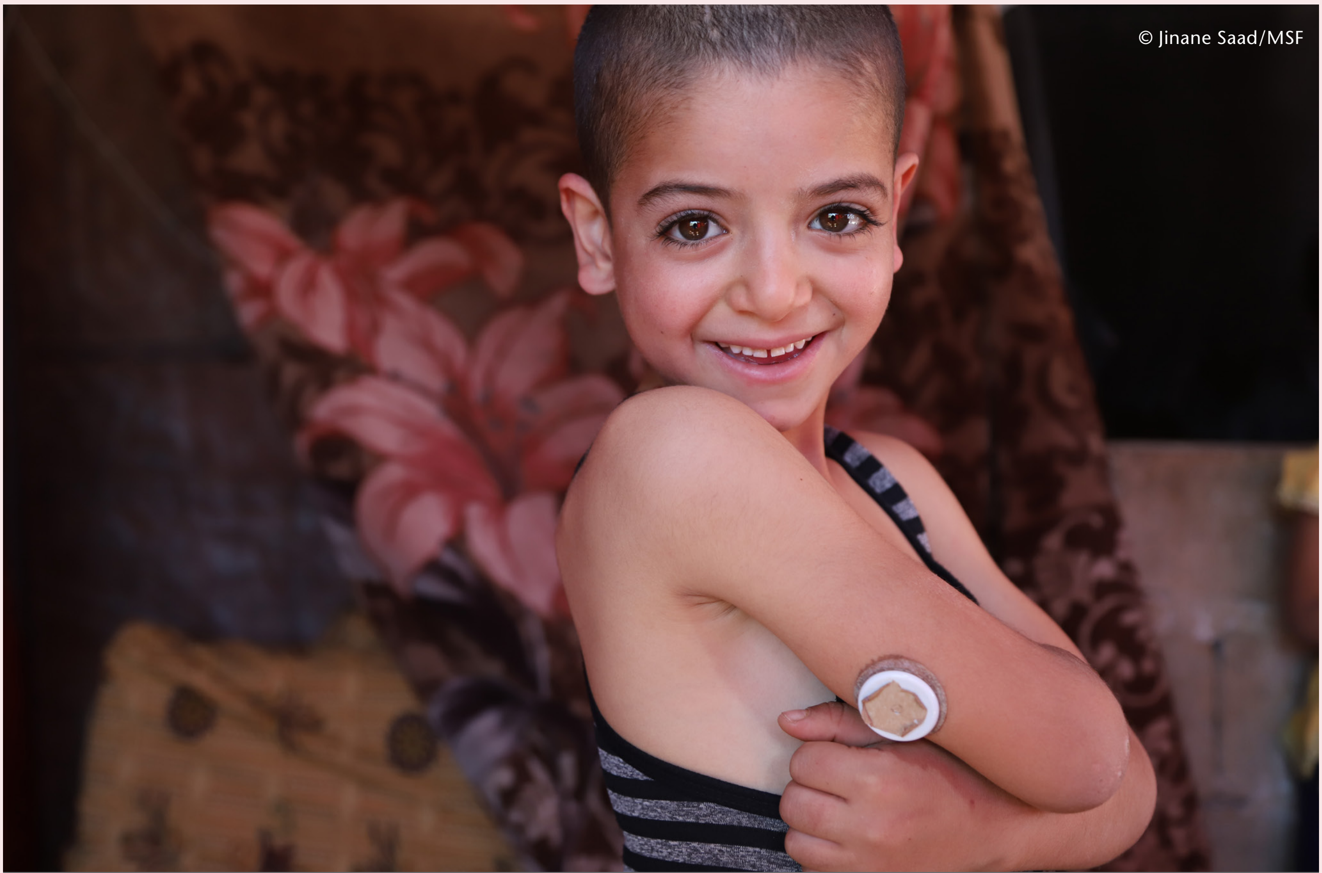
In many resource-limited settings where MSF works, such as South Sudan and within refugee camps, self-monitoring has not yet been implemented. This is due to a combination of challenges including poor availability of glucometers and the complexity of educating people how to use, interpret and document their readings.

Some glucometers may simplify this process, for example by having colour coding to demonstrate hypo- or hyperglycaemia. Mobile phone applications providing treatment recommendations to people based on glucometer readings may also improve care either through remote support or algorithm-based dose adjustments.

In high-income countries, glucose monitoring has moved towards minimally invasive and continuous monitoring devices. This eliminates painful multiple finger pricks and provides continuous glucose monitoring data that can be interpreted by the patient or health worker, including remotely.

Currently because of price, just one MSF project uses such a device: a transdermal patch which is replaced every two weeks – each priced at US$66. Data can be downloaded every eight hours by the patient. An alternative version allows data to be downloaded after two weeks. Accessing an increasing amount of blood glucose data requires more complicated interpretation by trained health workers, which can be supported through telemedicine or algorithm-based mobile application approaches.

Access and implementation of home glucose monitoring has been challenging; if prices of these new devices were lower, they could significantly simplify care and improve quality of life.



Khouloud, 13, attends an MSF-supported clinic in Bekaa, Lebanon, September 2019. When she fasted during Ramadan, she became very sick. She was taken to hospital and tested positive for diabetes. It was a big shock for her family. Khouloud struggled with having to prick herself multiple times a day to test her blood sugar levels. But she has since been given a glucose monitoring device.

Khouloud's mother:

"Using the monitor is much better than pricking her fingers three to four times a day. The monitor is much more comfortable. Khouloud does the injections, she scans the sensor, and checks on the results herself."

INNOVATION FOR ALL

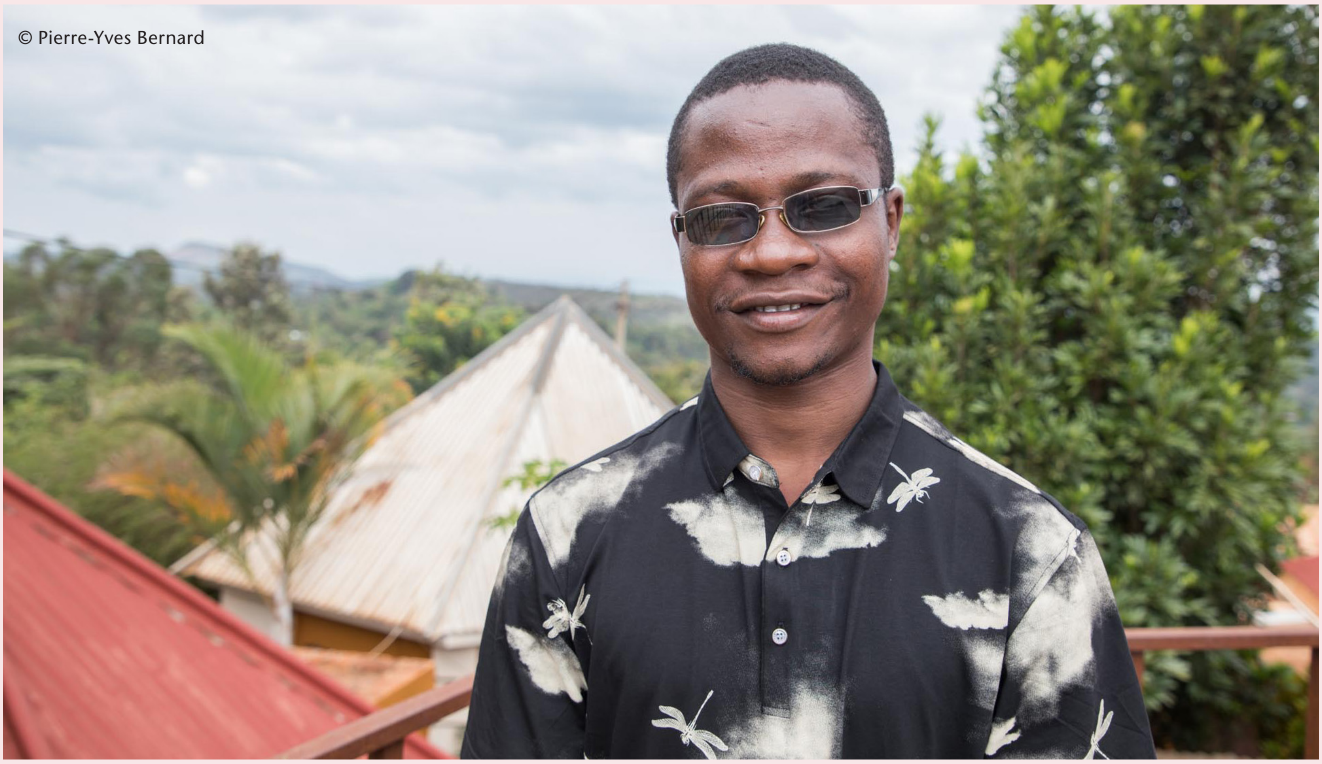
The pipeline for treatments and cures for diabetes is evolving fast. For T2D, a range of new oral treatments may delay the need for initiation of insulin, which would simplify delivery of care in humanitarian settings. New formulations of insulin such as tablets, long-acting injections or slow-release patches hold great potential for people living with diabetes in settings where MSF works.

One product under development known as "smart insulin" encapsulates insulin which is then only released when glucose levels are elevated, reducing the chances of dangerous hypoglycaemia as well as reducing the need for regular blood glucose monitoring. One such product developed through a biotech spinoff from the University of Bristol was sold to Novo Nordisk for US$800 million in 2018.[15]

Researchers and developers should ensure the innovation pipeline for diabetes medicines and insulin takes into account the needs of — and access for — people living with diabetes in resource-poor and humanitarian settings.

Dr Simon Masanja, Nduta Refugee Camp, Tanzania:

"If insulin could be delivered through a once-a-week injection, or even better through a patch, this would make such a massive difference in our setting. We don't have any paediatric endocrinology experts anywhere near, and educating our patients to self-inject is a real challenge. Even with knowing we can use local cooling devices, storage of medication is a challenge in the crowded huts especially during rainy season. If these developments are being investigated, we have to make sure they are affordable and available in settings like Nduta camp."



CONCLUSION AND RECOMMENDATIONS

In the last five years, MSF has cared for an increasing number of people with diabetes in need of treatment with insulin. These numbers are only set to further rise. In MSF NCD programmes, the number of people enrolled in diabetes treatment programmes may in some contexts be capped due to cost considerations of providing the proper package of care. And in many settings, the complexity of treatment itself remains the largest barrier to starting treatment for T1D. To make diabetes treatment more available, we need both insulin prices and feasibility of use to be addressed. To do this we urgently need the following:

- WHO and governments should ensure that people living with diabetes are included in the development of guidelines and implementation strategies.
- WHO should issue a consensus statement that supports the use of locally produced cooling devices for the storage of insulin and that dispels the notion that refrigeration is always needed to provide home insulin programmes.
- WHO and governments should work towards a high-level political resolution to endorse a commitment to provision of diabetes services, and establish mechanisms to fund the package of medicines, delivery and monitoring devices to provide adequate care.
- WHO should fast-track the prequalification process for biosimilar insulins, which was recently launched as a pilot programme. Pens and cartridge devices — not just insulin vials — should be included in the programme.
- Insulin must be affordable for people who need it. Corporations should provide transparent pricing that reflects the costs of production including for analogue insulin and insulin pen devices.
- Analogue insulins should be reconsidered for the WHO Essential Medicines List including quality-of-life data, and should be priced to reflect their cost of production.
- Research and development should ensure the diabetes pipeline takes into account the needs of people living with diabetes in resource-poor and humanitarian settings and includes access initiatives for new products.

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