

GPED Newsletter

Global Pediatric Endocrinology and Diabetes

*Keeping you up to date on Global Health
in Pediatric Endocrinology and Diabetes around the world*



Welcome to GPED's 14th Newsletter!



Dr J von Oettingen

Season's Greetings everyone!

I am excited to finish off the 2019 year with a packed newsletter that spans issues around essential medicines (pages 2 and 3), consequences of over-iodinization of salt in Chile (page 4), and the promotion of new growth charts for premature infants (page 5).

A major focus of this newsletter is access to life-saving medicines. I am particularly thrilled to see a little light at the end of the **insulin access crisis** tunnel. This comes at an opportune time where I just mentored a motivated group of McGill public health students who chose this topic for their first paper on "failures in global health". They investigated why Walmart's ReliOn insulin is not solving the access crisis – well, essentially, because it's just a distraction from the main issue, a band-aid on **soaring insulin prices** set by an oligopoly of 3 pharmaceutical companies that control 99% of the global insulin market. But as Jean-Pierre Chanoine is describing on pages 2 and 3, the World Health Organization is committed to promote affordable access to insulin and Biocon, an Indian company aims to produce a lower-cost biosimilar insulin.

Let's keep our fingers crossed, and our advocacy going!

As much as these news are encouraging, the scandal about **price-fixing of fludrocortisone** is all the more sobering, albeit not surprising (page 3). Whether it's insulin, fludrocortisone, or any other endocrine medication, we should be aware of the cost of the drugs we prescribe, pay attention and use our voices when the price does not seem right. As a testimony to our voices being effective, our and other's lobbying efforts just got **methimazole / carbimazole onto the WHO essential medicines** list, see page 4 for more details.

I also take this opportunity to ask that you consider **making a donation to GPED**. Every cent received as a result of this Holiday campaign will be used to provide life-saving medicines to children who do not have access to them either through advocacy or through donations.

The stories will all be told in the 2020 newsletters!

To donate, scroll down our homepage at <https://www.globalpedendo.org/>

Enjoy the read!!

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Mark your calendars: The 11th International Meeting of Pediatric Endocrinology will take place in Buenos Aires in 2021



IMPE2021

25-28 September | Buenos Aires

The "International Consortium for Pediatric Endocrinology" (ICPE) and the "Sociedad Latinoamericana de Endocrinología Pediátrica" will be organizing the **11th International Meeting of Pediatric Endocrinology (IMPE)** on **September 25-28, 2021** in Buenos Aires, Argentina.

Programs and Resources developed by GPED will be showcased at a special GPED exhibition Booth during IMPE.

Get involved! GPED welcomes Topics and ideas for the organisation of its annual symposium!

WHO launches the first prequalification program for insulin



Dr JP Chanoine

(Adapted by Dr Jean-Pierre Chanoine from: www.who.int/news-room/detail/13-11-2019-who-launches-first-ever-insulin-prequalification-programme-to-expand-access-to-life-saving-treatment-for-diabetes)

The World Health Organization (WHO) Prequalification Programme was set in 2001. Its objective was to facilitate access to medicines that meet unified standards of quality, safety and efficacy for HIV/AIDS, malaria and tuberculosis (<https://extranet.who.int/prequal/>)

On November 13, 2019, WHO announced the start of a pilot programme to prequalify **human insulin** to increase access to treatment for diabetes in low- and middle-income countries. This initiative is part of a series of steps WHO will take to address the growing diabetes burden in all regions. It is estimated that about 65 million people with type 2 diabetes need insulin, but only half of them are able to access it, largely due to high prices: “Diabetes is on the rise globally, and rising faster in low-income countries,” says Dr Tedros Adhanom Ghebreyesus, WHO Director-General. “Too many people who need insulin

encounter financial hardship in accessing it, or go without it and risk their lives. WHO’s prequalification initiative for insulin is a vital step towards ensuring everyone who needs this life-saving product can access it.”

Insulin prequalification can lead to lower prices. WHO prequalification of insulin is expected to boost access by increasing the flow of quality-assured products on the international market, providing countries with greater choice and patients with lower prices.

Insulin has been on WHO’s List of Essential Medicines since it was published in 1977. The most recent update of the Children’s list, released in 2019, includes: insulin injection (soluble) 100 U/ml in 10- mL vial; intermediate-acting insulin 100 U/ml in 10- mL vial (as compound insulin zinc suspension or isophane insulin).

Despite an ample supply, insulin prices are currently a barrier to treatment in most low- and middle-income countries. Three manufacturers control most of the global market for insulin, setting prices that are prohibitive for many people and countries. Data collected by WHO in 2016-2019 from 24 countries on four continents showed that human insulin was available only in 61% of health facilities and analogue insulins in 13%. The data showed that a month’s supply of insulin would cost a worker in Accra, Ghana, the equivalent of 5.5 days of pay per month, or 22% of his/her earnings. In wealthy countries, people often have to ration insulin, which can be deadly for people who do not get the right quantity of the medicine. A recent article by Ewen et al review the cost of insulin in 13 low- and middle- income countries (1). We have recently shown the difference in insulin cost in 5 African countries (2)

“Prequalifying products from additional companies will hopefully help to level the playing field and ensure a steadier supply of quality insulin in all countries,” says Dr Mariângela Simão, Assistant Director General for Medicines and Health products.

More than 420 million people live with diabetes. Diabetes is the seventh leading cause of death and a major cause of costly and debilitating complications such as heart attacks, stroke, kidney failure, blindness and lower limb amputations.

People with type 1 diabetes need insulin for survival and to maintain their blood glucose at levels to reduce the risk of common complications such as blindness and kidney failure. People with type 2 diabetes need insulin for controlling blood glucose levels to avoid complications when oral medicines become less effective as the illness progresses.

In addition to insulin prequalification, WHO will take several steps in the coming year to address the diabetes burden. Plans are underway to update diabetes treatment guidelines, devise price reduction strategies for analogues and improve delivery systems and access to diagnostics. WHO also works with countries to promote healthier diets and physical activity to lower people’s risk of developing type 2 diabetes.

References:

1. Ewen M, Joosse H-J, Beran D, et al. Insulin prices, availability and affordability in 13 low-income and middle-income countries. *BMJ Global Health* 2019;4:e001410. doi:10.1136/bmjgh-2019-001410
2. Rowlands A, Ameyaw E, Rutagarama F, et al. Insights from the WHO and National Lists of Essential Medicines: Focus on Pediatric Diabetes Care in Africa. *Horm Res Paediatr* 2018;90:82–92 (DOI:10.1159/000490467)

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The insulin manufacturer Biocon commits to decreasing the price of insulin by 70%

Biocon is an Indian manufacturer of biosimilars of insulin (www.biocon.com/). It presently markets a biosimilar glargine in Japan and in several low- and middle-income countries. It also sells biosimilar human insulin in several low- and middle-income countries. Biosimilar short-acting analogues of insulin are presently under development.

Kiran Mazumdar Shaw, chairperson and managing director at Biocon (and a philanthropist), announced on September 25, 2019, at a United Nations General Assembly (UNGA) side meeting on innovation and universal health access convened by UN-AIDS Health Innovation Exchange, that Biocon plans to bring down the cost of recombinant human insulin down, to 0.1 US\$ per day. This would represent a major decrease in cost for the patient and likely markedly increase access to human insulin.

Indeed, the high cost of insulin in low resource settings represents a major barrier to diabetes treatment. In a survey of 43 low income countries in 2015, the cost of a 10 ml vial (1000 units) of human insulin was found to be in average US\$7.64 in the public sector and US\$16.65 in the private sector, with a large variability between countries. Prices were cheaper for vials compared to cartridges/pen and for human vs analogue insulin. We recently reported observed a similar situation in 5 African countries.

The future will tell us how this initiative is developing and what effect it has on access to insulin for the child with diabetes.

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Anticompetitive behaviour: pharmaceutical companies colluded to increase the price of fludrocortisone by 1,800%

Fludrocortisone is a life-saving medicine that is well known to pediatric endocrinologists. It is used mainly for the management of salt-wasting congenital adrenal hyperplasia (SW CAH), and less commonly in children, for Addison disease. It is a synthetic analogue of aldosterone that was patented in 1953, some 56 years ago!

Fludrocortisone was included in the very first edition of the WHO Model List for Essential Medicines (EML) back in 1977. It was deleted in 2003 because of the rarity of Addison disease. In 2009, a joint submission by Drs G Warne (Royal Children's Hospital, Melbourne, Australia), J Raza (National Institute of Child Health, Karachi, Pakistan) and K Armstrong (Caring & Living As Neighbours, Australia) led again to the inclusion of fludrocortisone in the WHO EML for children (for the treatment of CAH), and, by extension (acknowledging the importance of this medicine for the treatment of congenital adrenal hypoplasia and adrenal failure in adults), in the WHO EML for adults.

Despite being included in the WHO EML, we have recently shown that it was present in only 29% and 48% of the National EMLs in Africa and in Latin America/Caribbean, respectively. In addition, even when included in the National EML, fludrocortisone, which is or should be a very affordable medicine, remains sometimes difficult to access.

The story reported by Iacobucci in the *British Medical Journal* is particularly sad: in short, ASPEN UK admitted in August 2019 that it took part in an anticompetitive arrangement by illegally paying two competitors in order to secure a monopoly for the distribution of fludrocortisone in UK. This resulted in a 1800% increase in the price paid by the National Health Services (NHS) in UK for fludrocortisone (from 1.5 to 30 GBP for 30 tablets of fludrocortisone).

In addition to paying a fine of 8 millions GBP, "Aspen has promised to ensure that in the future there will be at least two suppliers of fludrocortisone in the UK to help the NHS obtain better prices" (reference below).

We, pediatric endocrinologists, should keep an eye on the cost and availability of medicines in our countries and liaise with the appropriate organisations (government, parent's groups, hospital pharmacies..) to support affordable access!

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- Iacobucci G. Drug firms colluded to hike fludrocortisone price by 1800%, says watchdog. *BMJ* 2019;367:l5881
- Rowlands A, Ameyaw E, Rutagarama F, et al. Insights from the WHO and National Lists of Essential Medicines: Focus on Pediatric Diabetes Care in Africa. *Horm Res Paediatr*. 2018;90(2):82-92.
- Rowlands A, Acosta-Gualandri A, Guevara-Aguirre J and Chanoine JP. WHO and national lists of essential medicines in Mexico, Central and South America, and the Caribbean: are they adequate to promote paediatric endocrinology and diabetes care? *BMJ Glob Health*. 2016; 1(3): e000114

ESPE Yearbook 2019

Each, the European Society for Paediatric Endocrinology (ESPE) publishes a Yearbook with expert commentaries on the most important articles published over the last 12 months. Since 2016, the **Yearbook of Pediatric Endocrinology** includes a chapter on **Global Health for the Pediatric Endocrinologist** that is prepared by Drs. Julia von Oettingen and Jean-Pierre Chanoine. The 2019 edition is no different!



The full version of the yearbook can be found on Amazon (USD 11):

https://www.amazon.com/Yearbook-Paediatric-Endocrinology-2019-Ken/dp/1692760432/ref=sr_1_3?keywords=yearbook+ESPE&qid=1574977880&sr=8-3

It can also be accessed on line through the GPED website (www.globalpedendo.org) at www.espeyearbook.org. This year's chapter includes 17 articles and focuses on access to insulin, neonatal screening for congenital hypothyroidism, disorders of sexual differentiation and growth and development. **Enjoy the read!**

Methimazole/carbimazole are now included in the 2019 WHO Essential Medicines List as first choice for the management of Graves hyperthyroidism in children and adults



Dr JP Chanoine

Antithyroid drugs used in the management of Graves hyperthyroidism include propylthiouracil (PTU), methimazole and carbimazole. Between 1990 and 2008, in the USA, 23 cases of irreversible liver failure requiring transplantation (including 7 in the pediatric age group) have been identified following management of Graves hyperthyroidism with PTU. In contrast, no cases of irreversible liver failure were reported in patients treated with methimazole. As a consequence, in April 2010, the FDA added a Boxed Warning to the label for PTU, "... to include information about reports of severe liver injury and acute liver failure, some of which have been fatal, in adult and pediatric patients using this medication". As a consequence, PTU is no longer recommended as first line therapy in Graves' hyperthyroidism. PTU has long been the only antithyroid drug included in the WHO Model List of Essential Medicines (EML). Thanks to a submission by Dr JP Chanoine in the name of GPED, the 2019 revision of the WHO Model List of Essential Medicines now includes methimazole and carbimazole as first choice drugs for both children and adults. The Expert Committee:

...recommended the addition of methimazole with a square box to the core list of the EML and to the complementary list of the EMLc for the treatment of primary hyperthyroidism. Carbimazole is a therapeutically equivalent alternative. The Committee also recommended that the square box be removed from the listing of propylthiouracil on the EML. Propylthiouracil remains the recommended first-line treatment for women in the first trimester of pregnancy, and in patients for whom first-line treatment with methimazole (or carbimazole) is not appropriate or available. Propylthiouracil remains listed on the complementary list of the EMLc for use in patients for whom alternative first-line treatment is not appropriate or available

The listing is as follows (Section 18.7 of the EMLc):

□ methimazole*	Tablet: 5mg, 10mg, 20mg. * carbimazole is an alternative depending on local availability.
potassium iodide	Tablet: 60 mg.
propylthiouracil*	Tablet: 50 mg. *for use in patients for whom alternative first-line treatment is not appropriate or available

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- SA. Rivkees, DR. Mattison. Propylthiouracil (PTU) hepatotoxicity in children and recommendations for discontinuation of use. *Int J Pediatr Endocrinol.* 2009; 2009. doi: 10.1155/2009/132041
- EMLc: www.who.int/medicines/publications/essentialmedicines/en/

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Iodine salt fortification and prevalence of hypothyroidism: Update on Chile



Dr F Grob

Iodine deficiency (ID), one of the most common nutritional deficiencies worldwide, may cause goiter and endemic cretinism. As a result, during the last century, the international community has supported iodine fortification programs to reduce the risk of ID. While these programs were extremely successful, increasing iodine intake in a population with iodine deficiency was shown to also increase the risk of thyroid autoimmunity and of hyperthyroidism. Moreover, increased incidence of hypothyroidism has been described in the United States and Denmark almost after twenty years of the introduction of national mandatory iodine fortification programs (1).



Dr L Mosso

In Latin America, data on iodine status is scarce. In Chile, the prevalence of endemic goiter in schoolchildren was 25% in 1979, prompting the initiation of a salt fortification program with iodine, which led to the elimination of this condition in 1985. However, elevated median urinary iodine concentrations (UIC, median > 500 mcg/L) in schoolchildren were reported in 2000 (2). As a consequence, iodine content of the salt was reduced from 100 to 40 mg/kg (it is 45 mg/kg in the USA and 77 mg/kg in Canada). Ten years later, a national survey revealed a prevalence of hypothyroidism of 25% within the population. At this point, no changes to the iodine fortification program were made.

A new population survey performed in 2017 revealed a prevalence of autoimmune disease of 9.2% and of hypothyroidism of 24.1% (17.1% subclinical defined as a TSH greater than 5.7 and 4.2 mIU/L for subjects under and above 20 years old, respectively, with a normal free T4 according to the reference values of the laboratory assay used, and 7% overt hypothyroidism defined as a TSH above the reference range with a low free T4). Median UIC was 201 µg/L with a large variability. Prevalence of thyroid disease and UIC varied among the country but a robust correlation was observed between hypothyroidism and high UIC, reflecting higher salt consumption (up to 10 grams per day). Recently, similar numbers were found among Chilean pregnant women (3). Considering the amount of iodine in salt, the Chilean population has been exposed five times (from 1979 to 2003) and twice (from 2003) the iodine recommended by the World Health Organization (WHO) and this is associated with mild TSH elevations. Therefore, a new reduction in the amount of salt iodine fortification has recently been considered along with the creation of a national follow-up program.

In conclusion, iodine fortification in mildly deficient populations should be carefully implemented as it may increase the incidence of hypothyroidism even many years later. Possible mechanisms explaining this phenomenon might include an increase in the prevalence of thyroid autoimmunity and an increase in the production of iodine-containing derivatives of arachidonic acid in response to increased iodine intake as a means to protect against an iodine overload. Additionally, the obesity epidemic which is severe in Chile might contribute to the mild elevations in TSH. We suggest that population-wide mandatory iodine fortification should be maintained while monitoring its effects within the population. Policies towards the reduction of salt consumption should be encouraged, as well as dairy consumption and breastfeeding.

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3. Castillo C, Lustig N, Margozzini P, A Gomez A, Rojas MP, Muzzo S, Mosso L. Thyroid-Stimulating Hormone Reference Ranges in the First Trimester of Pregnancy in an Iodine-Sufficient Country. *Endocrinol Metab* 2019 Jun; 34 (2):213-214

Monitoring the postnatal growth of preterm infants: a paradigm change. International INTERGROWTH-21st Preterm Postnatal Growth Standards



Dr J Villar

Postnatal growth standards for preterm infants to monitor weight, length and head circumference should be based on a single cohort of preterm newborns (not fetuses) with known gestational age and no evidence of intrauterine growth restriction. At present, the postnatal growth of preterm infants is monitored with cross-sectional reference charts using measures taken only at birth, based on the idea that preterm infants should grow like fetuses. This is almost never achieved. In addition, when preterm infants are forced to grow postnatally like fetuses, their risk increases of becoming obese and developing metabolic syndrome later in life.

We recommend that the international INTERGROWTH-21st Preterm Postnatal Growth Standards should be used instead of reference charts to monitor the postnatal growth of infants born pre-term.

The standards were constructed following the same prescriptive approach (healthy mothers recruited early in pregnancy) and methodology as the WHO Child Growth Standards for term newborns (See GPED Newsletters Jan 2017 and Sep 2019). Optimal growth of preterm infants is best achieved by feeding with the mother's milk, which was promoted and supported for all infants contributing to the INTERGROWTH-21st Preterm Postnatal Growth Standards. The INTERGROWTH-21st Preterm Postnatal Growth Standards and the WHO Child Growth Standards merge at 6-months post-term. From that age onwards, the growth of preterm infants should be monitored using the WHO Child Growth Standards.

The cohort of newborns on whom the INTERGROWTH-21st Preterm Postnatal Growth Standards are based have been shown to have satisfactory health, nutrition and neurodevelopment up to 2 years of age (2). Such detailed follow-up of a cohort of preterm infants contributing to international standards has never been reported in the literature.

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Publications, apps, tables and other resources are available at: <https://intergrowth21.tghn.org/postnatal-growth-preterm-infants/>

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