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The First 1,000 Days: Trends towards Biosensing in Assessing Micronutrient Deficiencies

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Abstract : Micronutrients provide the essential building blocks for brain development, healthy growth and a strong immune system in children. Malnutrition in form of micronutrient deficiencies develop gradually over time and their negative effects are not seen until irreversible damage may have occurred. The World Health Organization (WHO) supports the 2016 Global Nutrition Report (GNR), emphasizing the enormous importance of investing in the critical first 1,000 days nutritional requirement as it directly affects the attainment of 12 out of the 17 United Nations (UN) Sustainable Development Goals (SDGs). Up till now, in many countries, early detection of malnutrition is carried out by specific, majorly blood-based tests in specialized laboratories by trained personnel. This review expatiates on diagnostic trends towards early detection of micronutrient malnutrition highlighting the significant role of Engineering in this cause. Focusing on the children within the 1000-day critical window, suggestions on modalities for continual tracking required to prevent malnutrition using biosensors are also advanced in this review.

Keywords: 1000 days; biosensor; early diagnosis; malnutrition; micronutrients; nutritional assessment; Sustainable Development Goals

1. Introduction

Nutrition during the first 1,000 days of life, starting from conception up to 2 years of age, has a major influence on the quality of health throughout the life of an individual. It represents a critical period, where the essential building blocks for brain development, healthy growth and a strong immune system are rapidly formed [1]–[4]. The impact of poor nutrition (malnutrition) during this time can be irreversible and has lasting effects that spans generations. Malnutrition broadly refers to macronutrient and/or micronutrient deficiencies. The UN World Food Programme (WFP) states that malnutrition at an early age leads to reduced physical and mental development during childhood, which can lead to further complications in adulthood. In fact, malnutrition is the largest single contributor to diseases in the world, according to the UN's Standing Committee on Nutrition (SCN) [5]–[8]. The following are key benefits of right nutrition to children within this 1000-day window [6], [8]:

- results in the healthy development of a child's brain and fuels growth.

- improves a child's preparedness for school and further educational achievements.
- reduces inequalities in health, education, and earning potential.
- reduces risk of developing non-communicable diseases such as diabetes and heart disorder later in life.
- saves more than one million lives each year.
- boosts a country's GDP significantly.
- breaks the intergenerational cycle of poverty.

The importance of childhood nutrition during this 1000-day critical window is further reflected by WHO's support of the 2016 Global Nutrition Report (GNR), pointing out the enormous importance of investing in the critical first 1,000 days nutritional requirement, which directly affects the attainment of 12 out of the 17 United Nations (UN) Sustainable Development Goals (SDGs) [9]. In fact, the UNSCN showed relationships between nutrition and all 17 SDGs [10], and Bill Gates stated "*An investment in nutrition can help make every other investment in health and development pay-off*" [11].

According to the 2016 GNR, compiled and reported by all the Global Nutrition Stakeholders (WHO, UNICEF, etc.), the key goal is to end malnutrition in all its forms by the year 2030. In 2016, global nutrition targets were set for 2025, which include reducing the number of stunted children in the world by 40% and reducing and maintaining child wasting below 5%. With concerted and strategic efforts such as exclusive breastfeeding, many countries are on course towards meeting the pre-defined targets as it relates to the indicators of malnutrition among children under five years of age. However, the number of stunted children under the age of five is declining in every region except Africa [9].

Of all African regions, West Africa alone accounts for half of the stunting increase in Africa; there were 4 million more stunted children in Western Africa in 2016 than in 2000 [12], [13]. West Africa also accounts for 33% of stunted children and 34% of severely wasted children in Africa. Nigeria, a West African country, is the most populous nation on the continent; ergo, solving this problem in Nigeria will have a significant effect on attainment of all WHO/UN set objectives in this regard, causing a ripple effect across the continent and the world at large. It's been established that there are 17.3 million severely wasted children worldwide and one in ten of all severely wasted children worldwide live in Nigeria [14].

Specifically, the GNR 2016 reports Nigeria to have a stunting prevalence of 32.9% (which signifies that the nation is off course, making very minimal progress towards the set goal), with a position of 98 out of the 132 ranked (from lowest to highest stunting prevalence) countries. Also, Nigeria has been reported to have a wasting prevalence of 7.9% (which signifies that it is completely off course towards the set goal), with a position of 93 out of the 130 ranked (from lowest to highest stunting prevalence) countries.

The overall global nutrition target of the WHO is "*to end malnutrition in all its forms*" [9], [15]. Though the 2016 GNR shows that not all countries have cases of malnutrition, ending malnutrition requires prevention of disease. Preventing malnutrition is driven by early diagnosis i.e. before a case is termed malnutrition. Therefore, targeted interventions in all its forms towards ending malnutrition is inevitable in order to attain the WHO goal and also ensure the benefits of proper nutrition as mentioned earlier. Figure 1 illustrates this goal with respect to children.

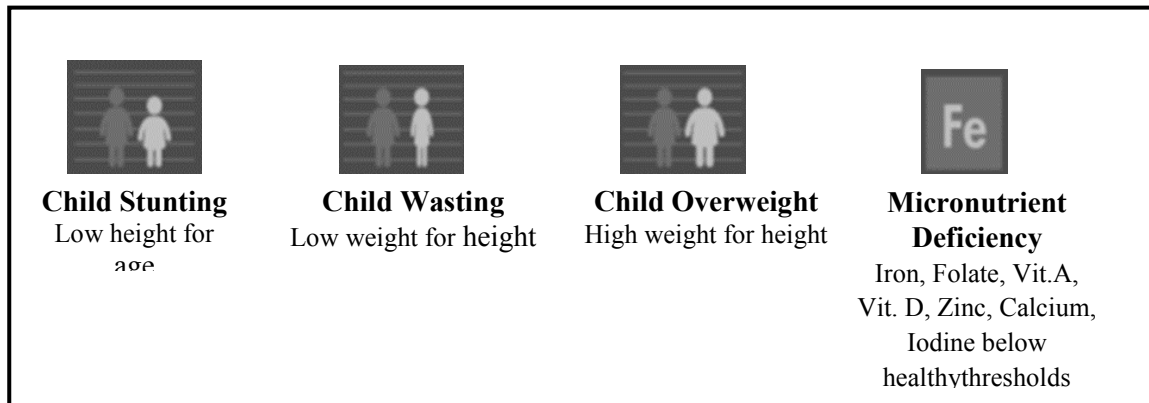


Figure 1: Malnutrition affecting Children [9]. Reproduced with permission from the International Food Policy Research Institute www.ifpri.org. The original table is available online at <http://ebrary.ifpri.org/cdm/singleitem/collection/p15738coll2/id/130354/rec/1>.

2. Micronutrients

Micronutrients refer to vitamins and minerals. They are the essential building blocks for healthy brains, bones and bodies. Micronutrient deficiencies result in weakened immunity, stunted growth, cognitive delays and certain diseases [16], [17]. While micronutrients are only required in small amounts in a child's diet, they can cause a less visible and often devastating form of malnutrition. Sometimes they are referred to as "*hidden hunger*" because even after a child is probably full and satisfied from a meal, the meal may still lack micronutrients. Lam and Lawlis[17] presented an extensive meta-analysis, which proves that micronutrients are very essential for brain development. Micronutrient deficiencies develop gradually over time and their negative effects are not seen until irreversible damage may have been done [16]–[19]; hence, the need for them to be continually monitored for early detection and timely intervention.

The following micronutrients have been identified as very important for child growth by WHO, UNICEF and Nutrition International (formerly known as Micronutrient Initiative Organization) [20]–[22]. It is believed that deficiency in one or more of them indicates deficiencies in some other secondary micronutrients.

- *Iron* – Iron deficiency is a widespread nutritional disorder affecting more people than any other condition, constituting a public health condition of an alarming proportion. It leads to impaired immunity and anaemia, which reduces the energy levels of those affected.
- *Vitamin A* – Vit. A deficiency causes severe visual impairment and blindness, it increases the risk of severe illness considerably and potentially causes death from common childhood infections such as diarrhoea and measles.
- *Iodine* – Iodine deficiency is the main cause of preventable brain damage or mental impairment in children. Its most devastating impacts occur during foetal development and in the first few years of a child's life.
- *Zinc* – Zinc deficiency impairs immunity and is also linked with an increased risk of gastrointestinal infections. In addition to Vit. A deficiency, it is also a contributing factor in child deaths due to diarrhoea.
- *Calcium* – Deficiency in calcium leads to poor bone density which may ultimately cause bony deformity such as rickets.

- *Vitamin D* – Vit. D deficiency can also cause calcium deficiency since it aids calcium absorption. Vit. D deficiency also causes delayed motor development in infants and like calcium deficiency may cause rickets.
- *Folate* (Vit. B9) – Generally, folate deficiency slows growth rate. Folic acid is required in high amounts in infants as it helps stimulate DNA replication and cellular growth.

Deficiencies in calcium, vitamin D and folate particularly are very serious issues during pregnancy and pose some health complications for both mother and growing infant.

3. Conventional Methods for Nutritional Assessment

The first important step of the 4-step Nutrition Care Process (NCP) is Nutrition Assessment, followed by Nutrition Diagnosis, Nutrition Intervention and Nutrition Monitoring/Evaluation. The goals of the NCP are:

- To identify individuals at risk of becoming malnourished.
- To identify individuals already malnourished.
- To develop initiatives/intervention programmes to fight malnourishment.
- To evaluate the effectiveness of already implemented initiatives and measures.

Presented here are the four widely known methods of measuring malnutrition (i.e. Nutrition Assessment) [23]–[25], the problems associated with each method, and some related work using these methods:

- a. Dietary evaluation methods – Nutrients intake assessment through methods such as 24-hour dietary recall, food frequency questionnaire, dietary history, food diary technique and observed and weighed food consumption. Some of the typical challenges of this method are: trained interviewers needed, information supplied by the patient may not be truly representative of his/her actual dietary intake, long and time consuming questionnaires. [26] presented a typical example of a food diary and food frequency questionnaire, used to assess the nutritional status and eating behavior of children aged 9 months to 3 years in the Ukraine. This study revealed a nutritional imbalance in the children with excess consumption of macronutrients and insufficient intake of micronutrients. More recently, [27] described the AutoDietary, a wearable which consists of a high-fidelity microphone worn on the neck to accurately record acoustic signals during eating in a noninvasive manner.
- b. Clinical methods – Clinical examination of body parts like hair, skin, nails, mouth, gums, tongue, eyes, muscles, bones & thyroid gland for physical signs known to be associated with macronutrient and micronutrient malnutrition. The major problem with this method is its incapability to detect malnutrition early.
- c. Biochemical/ Laboratory methods – Sample collection (e.g., blood, stool or urine) in the field and analysis in specialized laboratory setting to assess nutritional status and deficiencies. This offers a precise and accurate evaluation before any physical malnutrition signs appear. Some challenges with this method are: pain/complications from taking (blood) samples, requires specialized labs with specific equipment and trained lab personnel, high costs and time consuming.
- d. Anthropometric methods – Anthropometry refers to the scientific study of measurements obtained from the various parts of the human body, e.g., to measure specific parts of the human body to validate suspected malnutrition. The most common anthropometric measurements are: height, weight, mid-upper arm circumference (MUAC) and head circumference; additional parameters collected are age, gender and presence/absence of oedema in children. Based on these measurements, three important anthropometric indices are drawn, which are used to indicate categorically the presence or absence of malnutrition:
 - Weight-for-height – Low weight-for-height signifies wasting while high weight-for-height signifies overweight.

- Height-for-age – Low height-for-age signifies stunting.
- Low weight-for-age could mean the child is underweight while High weight-for-age points to Obesity.

The weight-for-height, height-for-age and weight-for-age are thereafter interpreted using the Z-score classification system, which expresses the anthropometric value as a number of standard deviations (SD) or Z-scores below or above the reference mean or median value. The WHO Global Database on Child Growth and Malnutrition [28] uses a Z-score cut-off point of <-2 SD to classify low weight-for-age, low height-for-age and low weight-for-height as moderate and severe malnutrition, and <-3 SD to define severe malnutrition. The cut-off point of $>+2$ SD classifies high weight-for-height as overweight in children. In addition, all cases of oedema are classified as severe malnutrition and the MUAC is regarded as a rapid and effective predictor of risk of death in children aged 6 to 59 months [29], [30]. Some of the issues associated with this method are measurement errors and the inability to detect when nutrient levels fall below healthy thresholds – it is only able to tell when a child is regarded as malnourished.

In [31], the authors described the use of anthropometric method to detect malnutrition in children in Malawi. These measurements were taken at designated healthcare facilities by the health workers and then sent via text message to a central server where the information is analyzed for indicators of malnutrition. Where malnutrition is detected, instant feedback messages are sent to the health worker stating actions to be taken concerning the malnourished child. The authors in [32] pointed out the importance of accurate anthropometric measurements, stating that errors in reading and/or recording negatively affects the quality of healthcare; they described a means of electronically measuring and recording potentially malnourished children's MUAC. [33] addressed the difficulty of anthropometric measurements in rural areas – complications in transporting bulky and heavy equipment, which must be properly and adequately calibrated. Image processing techniques, enabled the authors to estimate anthropometric indices based on the measurements obtained from a set of body part images and its relations with the child's gender and age.

Among these four, the biochemical/laboratory testing method is known to be most accurate with the capabilities to detect the early onset of malnourishment but its requirements makes frequent monitoring unfeasible.

4. Biosensors

Sensors have become vital components for real-time monitoring. Currently, sensors are ubiquitous; they are low cost devices and utilized in nearly every sector of life [34], particularly in health monitoring as usually the first point of contact in a health monitoring system. Their application ranges from temperature, pressure, humidity, flow, optical and acoustic measurements.

Simply put, biosensors miniaturize the entire biochemical/laboratory methods of testing into portable, Lab-on-a-chip (LOC) devices that can be used in POC settings. The aim of biosensors is to detect the presence and/or concentration of target analytes (biomarkers) in a given sample, which are representative of the health condition being analyzed. Biosensors (biological sensors) have been identified to provide accurate/precise information on the measured health indices as well as early indication of diseases [35], [36]. Among the different types, molecular-based biosensors which use biological active elements such as enzymes, antibodies and whole cells as the receptor elements (bioreceptors) produce the highest selectivity [37]. Using advanced technologies, biosensors are able to detect biochemical changes in the body at the subclinical on-set of diseases. As illustrated in figure 2, the biosensors can measure certain biomarkers in body fluids, infected cells and/or their immediate environment to detect the biological changes due to disease.

Biosensors, have been proven to require low power, be cheaper, and less time consuming than laboratory-based biochemical methods of early diagnostics. For example, to test for the 7 micronutrients listed in this paper, a certain laboratory in Lagos Nigeria charges approximately \$430, and tests for Vitamin A and Vitamin D takes up to 6 weeks for the results to be ready. In contrast, Lee et al. [38] tested a LOC device for Vit. A and Iron analysis, which readily prepares results within a few minutes with expected costs of about \$1 per biomarker for each micronutrient.

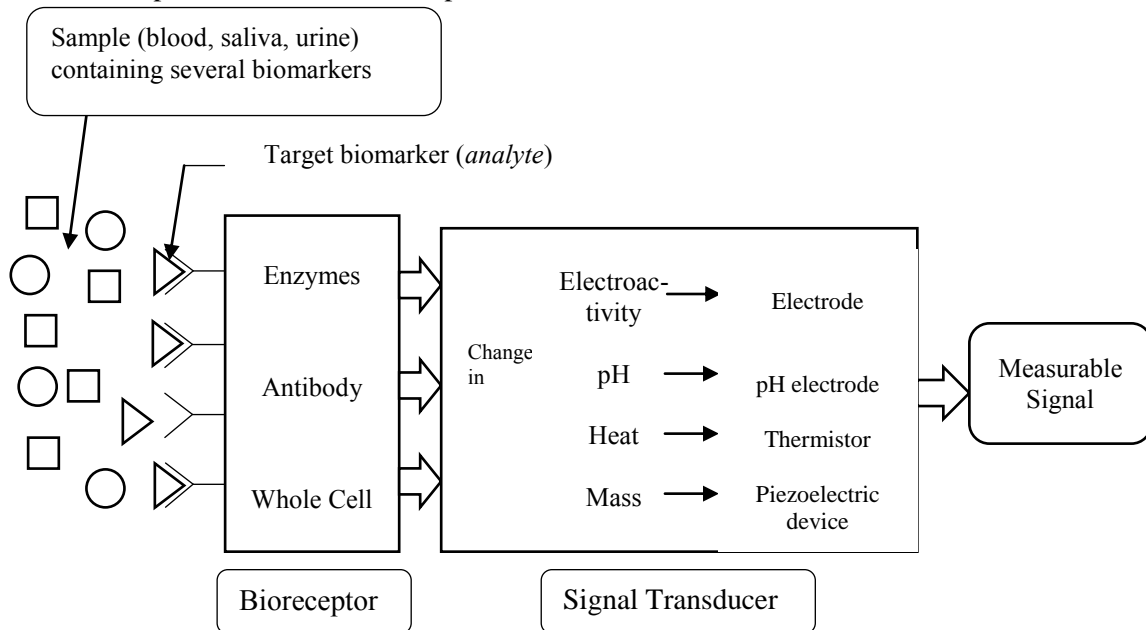


Figure 2: Principle of Operation of a Biosensor.

Partners representing the global food and nutrition enterprise created the BOND (Biomarkers of Nutrition for Development) Program to meet the growing needs for discovery, development, and implementation of reliable and valid biomarkers to assess nutrient exposure, status, function, and effect. Nutrition biomarkers are still undergoing extensive research under this program but so far a number of reports and publications have been done highlighting recent findings and also to define nutrient concentration in different sample fluids in order to make unbiased nutritional diagnosis [39]–[43]. However, it is important to note that the concentration of biomarkers in body fluids are affected by several factors; therefore, considerations must be made to accommodate these factors in making nutritional diagnosis. Some of these factors include but not limited to: presence of infection or disease, use of drugs, food activities in the body (digestion, absorption, metabolism, storage, excretion), physical activities and certain environmental factors [44].

Nutrition Biosensors: Some Related Works

Presented in Table 1, are several nutrition biosensors that have been designed, as found in literature. With a focus on research within the last six years, a search was conducted majorly on the ScienceDirect database and then a general Google search.

Table 1: Literature search on micronutrient biosensors

| Ref | Micronutrient | Biofluid | Biomarker | Description |
|------|-------------------------|------------------|-------------------------------------|---|
| [38] | Vitamin D | Serum | 25(OH)D | Colorimetric detection & quantification of 25(OH)D using a novel gold nanoparticle-based immunoassay. |
| [45] | Iron, Iodine | Serum | Ferritin, Thyroglobulin | Fluorescence detection & quantification of ferritin, thyroglobulin & other proteins in complex elastomeric microfluidic devices. |
| [46] | Iron | Whole blood | Ferritin | The biosensor comprised of a lateral flow immunoassay (LFIA) test strip to perform on-chip sample preparation (to derive serum), antigen-antibody binding as in [38] to produce a colorimetric change. The LFIA test strip is inserted into an accessory where the colorimetric image is captured by a CMOS camera and analyzed by the developed mobile app to produce the required quantification. |
| [47] | Vitamin B12 | Whole blood | Not specified | On-chip sample preparation to derive plasma; a novel spacer pad to allow thorough antigen-antibody binding before colorimetric detection as done in [38]. |
| [48] | Vitamin A, Iron | Whole blood | RBP, Ferritin | On-chip sample preparation using a μ PAD to derive plasma; quantification was done by measuring light transmission (colour) changes by a photodetector. Result information was stored on an EEPROM and transmitted through NFC to a mobile phone application developed for this purpose. The application geo-tags the data and transmits it to a remote server for real time tracking of micronutrient deficiencies. They also added capability to detect CRP to check for inflammation caused by infection as this affects the results obtained. |
| [49] | Vitamin A, Iron | Serum | RBP, Ferritin | Their system consists of a reusable reader with a fluorescence imaging system and a disposable novel fluorescence test strip. Unlike their work in [46] that used LFIA, an incubation pad was used in the test strip to allow immediate sample-antibody interaction as soon as sample is introduced. |
| [50] | Zinc | Serum/ Plasma | N/A | This is a patent that presents a pigment-based micronutrient biosensor, removing the need for quantification. The result is obtained by naked-eye-observation of the pigment which is indicative of the concentration range. Although the emphasis was on Zinc, this biosensor can be implemented for Iron, Vit. D, Vit. B12, Iodine, Folate & others. |
| [51] | Iron | Serum | Ferritin | Iron-oxide nanoparticles was used novelly to enhance detection sensitivity of photonic crystal biosensors to quantify Iron by tracking peak wavelength value changes. |
| [52] | Iron deficiency anaemia | Serum | Soluble Transferrin receptor (sTfR) | Advancing from their work in [51], iron-oxide nanoparticles were functionalized with sTfR antibody and used as magnetic immuno-probes. |

| | | | | |
|------|--|--------------|-----|---|
| | | | | This resulted in increased signal to noise response of the photonic crystal biosensor for accurate and reliable determination of sTfR in serum. |
| [53] | Vitamin B1 (Thiamine) | Serum, Urine | N/A | Silver nanoparticles surface modified by glutathione (GSH-AgNP) was used to achieve visual colorimetric detection of Vitamin B1. This colorimetric detection actually reflects as changes in surface plasmon resonance and aggregation that occurs upon contact of Vitamin B1 and the GSH-AgNP. |
| [54] | Folate | Serum, Urine | N/A | A selective electrochemical mediator was synthesized and used at the surface of a carbon paste electrode zinc-oxide-carbon nanotube composite for a simple and rapid voltammetric detection & quantification. |
| [55] | Folate | Serum | N/A | A case was presented for a sensitive and selective determination of folic acid in the presence of an important interferent – Ascorbic Acid. The sensor was developed by modifying glassy carbon electrode with α -Fe ₂ O ₃ nanofiber. |
| [56] | Folate | Urine | N/A | A novel electrochemical sensor was developed – Graphene was deposited on zinc-oxide nanowire array that had been grown on graphene foam. The resulting sensitive hybrid detected Folic acid in the presence of an interferent – uric acid. |
| [57] | Vitamin B2 (Riboflavin), Vitamin C (Ascorbic Acid), Folic Acid | Plasma | N/A | Simultaneous electrochemical detection and quantification of the 3 micronutrients using a novel modified glass carbon electrode. The biosensor was able to selectively detect each micronutrient even at high concentrations of the others. |

5. Summary and Recommendations

Although, global nutrition targets have been set for 2025, the main target is to end malnutrition in all its forms by 2030. In order to end malnutrition it must be prevented; preventing malnutrition may take different forms including efforts from the agricultural base. Preventing malnutrition also requires detecting it early enough for intervention to be carried out before it is termed malnutrition. In addition, the GNR highlights scarcity of data which prevents identification and learning from real progress at global and national levels. Therefore, provisions must be made for easy and continuous measuring/monitoring of nutrition status.

As observed in Table 1, the bio-fluid used as test sample for almost all nutrient tests is blood or its derivatives (serum, plasma). Focusing on the children within the 1,000-day critical window, it is impractical to draw blood as frequently as possible as it is necessary for continuous monitoring of nutritional status. Therefore, there remains a huge gap in conveniently, promptly and accurately detecting when these important nutrients (micronutrients) fall below healthy thresholds in the body of children within this reference age bracket; the keyword being *conveniently*.

The problems associated with micronutrient deficiencies and the current methods for early and convenient detection are:

- The clinical signs of malnutrition in the form of micronutrient deficiencies are less visible compared to macronutrient deficiencies, such that they do not produce these signs or symptoms until severity has been reached – already referred to as malnutrition.
- The consequences of prolonged micronutrient deficiencies include those of macronutrients as well as weakened immunity, cognitive delays and diseases.
- Early detection can only be accurately and precisely diagnosed using biochemical indicators lab-tested through body fluids. These tests are usually time consuming and expensive. They require specialized equipment and trained personnel to interpret readings.
- Using blood as the test sample is characteristic to most of these tests but retrieving blood from children proves to be a painful/traumatizing process for them and difficult for the Phlebotomist.

The following suggestions/recommendations would aid in achieving continuous monitoring. A generic methodology for this process is also presented in figure 3.

- The development of micronutrient biosensors based on body fluids that are easier to collect such as urine, saliva or sweat. Specifically, many years of research on saliva confirms it contains abundant biomarkers like blood, and is able to facilitate early detection of diseases [58]–[68]. Table 2 presents some references to biochemical-based testing research works, proving the presence of nutritional biomarkers in saliva, and in some cases, how they correspond to serum-based measurements. Some disparities with results/conclusions from related works were noticed and mentioned in the result discussion column. The review conducted showed that there is very limited literature on the behaviour/characteristics of nutritional biomarkers in saliva of children within the first 1,000 days; therefore, thorough investigation in this area as well as research on its accuracy and reliability, will advance the possibility of saliva-based biosensors for this category.
- The biosensors should be very simple devices that can be used at the POC. This means they should be low cost, small in size, safe to use and results should be easily interpretable. Importantly, the biosensors must not require sample preparation or other special conditions for use.
- Furthermore, if integrated with a location mapping module and data transmission capabilities, such that somewhat anonymous test results are sent to a central database managed by an organization such as WHO or UNICEF, better targeted interventions can be carried out.
- Common micronutrient deficiencies within certain geographic regions as indicated by the location mapping modules will also help to determine the root causes of these deficiencies e.g. lack of soil required to grow Iron or Folate-providing foods.

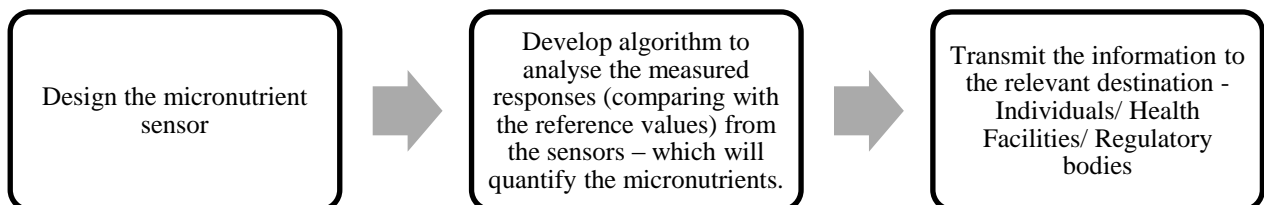


Figure 3: Overview of Nutrition Biosensor Development Process.

Table 2: Related works highlighting the presence of micronutrients in human saliva – focusing on the micronutrients highlighted in this review.

| Micronutrient | Ref | Ages of Participants | Results Description |
|----------------------|------------|---|--|
| Iron | [69]–[71] | 6 – 25 years for [69]; 8 months – 10 years for [70]; 8 – 14 years for [71]. | [69]showed a corresponding decrease in salivary ferritin with serum in iron-deficient subjects. [70], [71] showed increased salivary ferritin in contrast with decreased serum ferritin in iron-deficient subjects. |
| Vitamin A | [72]–[74] | 17 – 59 years for [72]; about 40 years for [73]; 20 – 40 years for [74] | Strong correlation between serum and salivary Vitamin A in the subjects in [72] and [74]. [73]demonstrated the presence of Vitamin A in saliva. |
| Iodine | [75]–[77] | Adults for [75], [77]; 35 – 68 years for [76] | The absolute salivary iodide was proportional to plasma inorganic iodine level in [75]. [77]showed that serum inorganic iodine and salivary iodine concentrations correlated under certain conditions. |
| Zinc | [78]–[81] | 12 – 13 years for [78]; primary school aged children for [79]; not specified for [80]; adults for [81] | No significant correlation between serum/plasma and salivary zinc noticed; zinc was present in all saliva samples. |
| Calcium | [82]–[86] | >18 years for [82]; 20 – 30 and 60 – 80 years for [83]; 6 – 12 years for [84]; 30 – 45 years for [85]; 20 – 45 years for [86] | Significant correlation between salivary and serum calcium levels in [86]; others signify presence of calcium in saliva. |
| Vitamin D | [87], [88] | 21 – 44 years for [87]; 18 – 48 years for [88] | Both studies are positively inclined towards using saliva for Vitamin D testing. They did not study correlation with serum/plasma. |
| Folate | [89]–[91] | Mean age of 49 for [89]; 25 – 30 years for [90]; majorly 25 – 35 years for [91] | [89]showed lower concentration of folate in saliva than serum. Results from [90] showed significant correlation between serum and salivary folate in the subjects. [91]simply quantifies the presence of folic acid in saliva. |

6. Conclusion

The goal of ending malnutrition in all its manifestations is of global import. Malnutrition is not the problem of the poverty stricken or the uneducated alone, as it has been observed. Governments all over the world are strengthening national commitments towards the eradication of malnutrition in their respective countries, by apportioning significant funds to the cause. In-depth research spanning several years has been done for blood and its derivatives with respect to nutrient concentrations producing consistent results; hence, the development of several nutrition biosensors in this regard, as reviewed in

Table 1. As mentioned in the recommendations in this paper, thorough investigations on the characteristics/ behavior of micronutrients in non-blood samples from children within the first 1,000 days is highly needed. Based on consistency and reliability obtained from the results of such investigations, the development of a nutrition biosensor to *easily/conveniently, accurately and promptly* detect micronutrient deficiencies in children will provide a more practical method of measuring malnutrition for children generally, within and beyond this 1,000-day window. It will also contribute positively to the sustainability of the WHO goal of ending malnutrition by 2030.

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