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Difference between Kwashiorkor and Marasmus: Comparative meta-analysis of pathogenic characteristics and implications for treatment

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Abstract

Kwashiorkor and marasmus are two clinical syndromes observed in severe acute malnutrition. In this review, we highlighted the differences between these two syndromes by reviewing the data comparing kwashiorkor and marasmus in literature, combined with recent microbiological findings and meta-analysis. Depletion of antioxidants, vitamins and minerals were more severe in kwashiorkor than marasmus. This was consistent with the severe and uncontrolled oxidative stress associated with the depletion of gut anaerobes and the relative proliferation of aerotolerant gut pathogens. This relative proliferation and invasion of gut microbes belonging to the aerotolerant *Proteobacteria* phylum and pathogens suggested a specific microbial process critical in the pathogenesis of kwashiorkor. Liver mitochondrial and peroxisomal dysfunction could be secondary to toxic microbial compounds produced in the gut such as ethanol, lipopolysaccharides and endotoxins produced by *Proteobacteria,* particularly *Klebsiella pneumoniae*, and aflatoxin produced by *Aspergillus* species. The gut-liver axis alteration is characterised by oedema and a fatty and enlarged liver and was associated with a dramatic depletion of methionine and glutathione, an excessive level of free circulating iron and frequent lethal bacteraemia by enteric pathogens. This was consistent with the fact that antibiotics improved survival only in children with kwashiorkor but not marasmus. The specific pathogenic characteristics of kwashiorkor identified in this review open new avenues to develop more targeted and effective treatments for both marasmus and/or kwashiorkor. Urgent correction of plasma glutathione depletion, alongside supply of specific essential amino acids, particularly methionine and cysteine, early detection of pathogens and an antibiotic more efficient than amoxicillin in supressing gut *Proteobacteria* including *K. pneumoniae,* and probiotics to restore the human gut anaerobic mature microbiota could save many more children with kwashiorkor.

Keywords: severe acute malnutrition, marasmus, kwashiorkor, children, protein, antioxidants, microbiome

1. Historical perspective and current status of knowledge

Marasmus has been described for the longest as the typical form of severe malnutrition; it was referred to as phthisis, dystrophy and cachexia. Oedematous malnutrition was first described in Latin America during the 19th century in several unobtainable publications cited by Autret and Béhar (1). The first publication to include typical pictures was from the French literature in 1913 by Guillon, where the syndrome was called "Bouffissure d'Annam" or swelling disease of Vietnam (2). Twenty years later, Dr. Cicely Williams, in her work in the colonial Ghana described this disorder as "a nutritional disease of childhood associated with a maize diet" and named the condition "Kwashiorkor" (3,4).

At the first session of the Joint Food and Agriculture Organization (FAO)/World Health Organization (WHO) Expert Committee on Nutrition in 1949, kwashiorkor was considered to be of widespread concern in developing countries and investigation was recommended (5). Thus, during the early 1950s, Brock and Autret carried out a survey in Africa. They reported that cases of kwashiorkor occurred in the twelve nations visited (belonging to all regions of sub-Saharan Africa namely central, west, east and southern Africa) and provided a clear description of its major signs and symptoms (6). The main conclusion was that kwashiorkor appeared to be related to a low protein diet, usually in weaning infants with clinical features including oedema, skin and hair dyspigmentation and fatty infiltration in liver, confirming the description of Dr. Williams in 1933 (3). The report by Brock and Autret was followed by a similar WHO/FAO study by Waterlow and Vergara on kwashiorkor in Brazil (7). They mentioned in their report that cases of "Sindrome Policarencial Infantile" (the name of kwashiorkor in Brazil) was found as an apparently identical form to the African syndrome. However, several cases were assessed as intermediate stages with less defined characteristics and variable manifestations such as

"wasting and oedema but normal liver" or "stunting and hair dyspigmentation but no oedema" (7).

This suggested coexistence between kwashiorkor and marasmus. Indeed, previously in 1953, the third session of the joint FAO/WHO Expert Committee on Nutrition (8) recognized the possible existence of intermediate cases between kwashiorkor and marasmus. According to this Committee, marasmus, which was called "severe undernutrition", related to a prolonged insufficient diet with reduced carbohydrates and fat (besides protein deprivation) and was distinct from kwashiorkor which was "protein malnutrition" due solely to an inadequate protein intake (8). After stating that the problem of definition was "without descriptive significance", the Committee then highlighted the need to determinate a proper terminology in defining the diagnostic characteristics of kwashiorkor and marasmus; as well as the importance of a detailed description and an administrative practice guideline to ultimately solve this problem (8). During the same year, at the 3rd session of the Joint FAO/WHO Expert Committee, a conference about protein malnutrition was held in Jamaica; they considered how to give accurate descriptions of the conditions, the classification for kwashiorkor, and the definition of the terms "kwashiorkor", "marasmus" and "marasmic-kwashiorkor" (9). The conference could not reach a consensus (9).

In 1959, Rao conducted his survey on protein malnutrition in 10 areas in Southern India and observed that the prevalence of kwashiorkor represented only 1% among children, but marasmus was observed in nearly twice as many children as kwashiorkor – 1.7% vs 1% (10). He stated that it was not "uncommon" to find intermediate types in one child which were frequently related to diets deficient in both calories and protein (10). In the early 1960s, the 6th session of the Joint FAO/WHO Expert Committee considered the importance of marasmus and confirmed that all aspects of the problem of protein-calorie-deficiency disease should be assessed "without decreasing the interest in kwashiorkor" (11). The Committee

also proposed a classification of nutritional diseases based on the nutrient deficiencies and clinical signs (11). Accordingly, kwashiorkor and marasmus were two main categories of a "new" condition termed "protein-calorie" malnutrition. In 1966, McLaren stated that the distinction between kwashiorkor and marasmus was important (12). Especially, he mentioned that kwashiorkor tended to occur in children aged 1-4 years of age whereas marasmus occurred most frequently in those under 1 year of age (12) and thereby, the focus should be placed on the younger age group.

In 1970, the Wellcome Trust sponsored a meeting to try to resolve the question of definition. It was agreed that the term kwashiorkor should be confined to those children with oedema and marasmus to those with a low weight for age; marasmic-kwashiorkor was used for children with a low weight-for-age and oedema. Hair, skin and liver signs were not used in the definitions (13). It was refined by Waterlow in 1972 by replacing weight-for-age with weight-for-height (14) as low weight-for-age included children who were stunted as well as emaciated (15). These definitions have been generally accepted and are those currently recommended by WHO using their latest anthropometric standards. Some countries, such as India and Mexico have used different classifications, and the severity of marasmic cases has changed as new anthropometric standards have been introduced. In some publications, kwashiorkor and marasmic-kwashiorkor have been combined and are then termed "oedematous malnutrition".

However, even though many studies had focused on these definitions, in practice there is often a marked overlap between the other symptoms and signs common in severely malnourished children. This makes our understanding of the pathophysiology and aetiology of these two forms of severe malnutrition incomplete. In this review, we attempted to point out the potential specific features of kwashiorkor and marasmus by reviewing the data comparing kwashiorkor and marasmus. It should be emphasised, however, that the two types

of cases reported in the literature are normally differentiated on the basis of oedema and anthropometry solely; none of the studies have further classified the patients into those with or without hair, skin or hepatic abnormalities, accompanying stunting or other clinical features (except over infection in some reports).

2. Methods

In this review, we searched papers from PubMed and Google Scholar in accordance with the PRISMA statement (**Checklist S1**). The search terms were used are kwashiorkor OR "protein malnutrition" OR "oedematous malnutrition" OR "marasmus" OR "non-oedematous malnutrition". We reviewed all observational studies including cohort studies, case-control studies, randomized control trials, cases report with at least one case of kwashiorkor and one case of marasmus as well as studies comparing kwashiorkor and marasmus until the last searched date on October 31st, 2019. In addition, since the late 1940s, three United Nations (UN) agencies - FAO, WHO, and United Nations Children's Fund (UNICEF) with their expert committees substantially contributed to the evolution of nutritional science and addressed nutritional deficiencies in developing countries. Thus, reports from FAO, WHO and UNICEF official websites were collected as a support source. We selected the Joint FAO/WHO Expert Committee on Nutrition as well as reports from authors who worked for FAO and WHO such as Autret, Béhar, Waterlow and those at INCAP (Institute of Nutrition of Central America and Panama), particularly Scrimshaw.

Next, random-effects meta-analysis was performed using Revman 5.3 software (16), using a different weighting scheme that depends on the risk difference measure for dichotomous outcomes and on the mean difference measure for continuous outcomes. Here, we defined 4 grades of quality of evidence for each characteristic analysed by meta-analysis to examine items that were potentially specific for one or other of the two conditions **(Table 1).** Grade A included characteristics which were assessed in at least 2 studies with more than

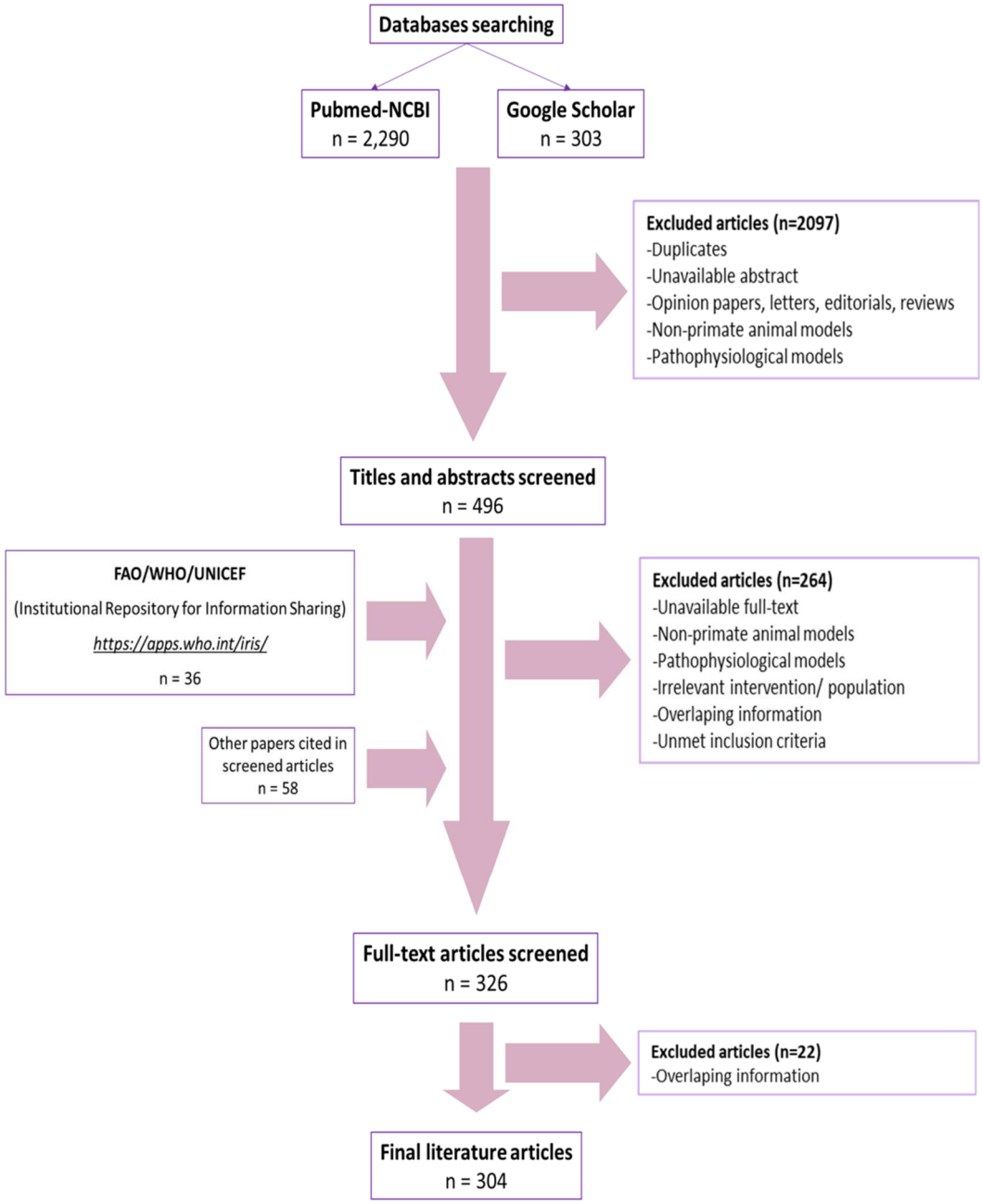
80% results with a consistent direction of effect (decreased/increased in kwashiorkor/marasmus) and a significant summary effect ($p<0.05$). Grade B was composed of characteristics which were also assessed in at least 2 studies with more than 80% consistent results, but the meta-analysis results didn't reach significance. Grade C listed the characteristics of which the data were available only in one study and the results were reported to be significant. Last, characteristics assessed in at least 2 studies with less than 80% consistent results were all classified in Grade D. Particularly, Grades A, B and C were divided into 2 sub-groups: specific characteristics (which occurred only in kwashiorkor or marasmus) and non-specific characteristics (which occurred in both kwashiorkor and marasmus but were more pronounced in one form compared to the other). All data collected are listed in **Suppl. Table S1** and summed with meta-analysis classification in **Table 1** (for specific characteristics) and **Suppl. Table S2** (for non-specific characteristics).

For quantitative analysis, the risk of bias assessment in each included study was performed following the Cochrane risk-of-bias assessment tool. Consequently, we classified each included study as 'low risk', as 'high risk, or as 'unclear risk', with the last category indicating lack of information. Risk of bias domains for intervention trials were random-sequence generation (selection bias), allocation concealment (selection bias), blinding of participants and personnel (performance bias), blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), selective outcomes reporting (reporting bias), and other potential sources of bias (**Suppl. Figure S1**). All figures were generated using RevMan 5.3 software.

3. Results

Over 2,200 articles were collected, of which ~600 articles met the inclusion criteria for full text review articles, 36 articles added from FAO/WHO/UNICEF, 58 articles cited in the screened articles. Finally, 304 articles were included in this review including 88 for quantitative analysis after excluding duplicates, articles reporting overlapping information or irrelevant studies such as non-primate animal models and physiopathological models (**Figure 1**). Risk of bias of each study were presented in **Suppl. Figure S1-S2** and **Suppl. Table S3**.

154 **Figure 1: Flow-chart showing the results of literature research**



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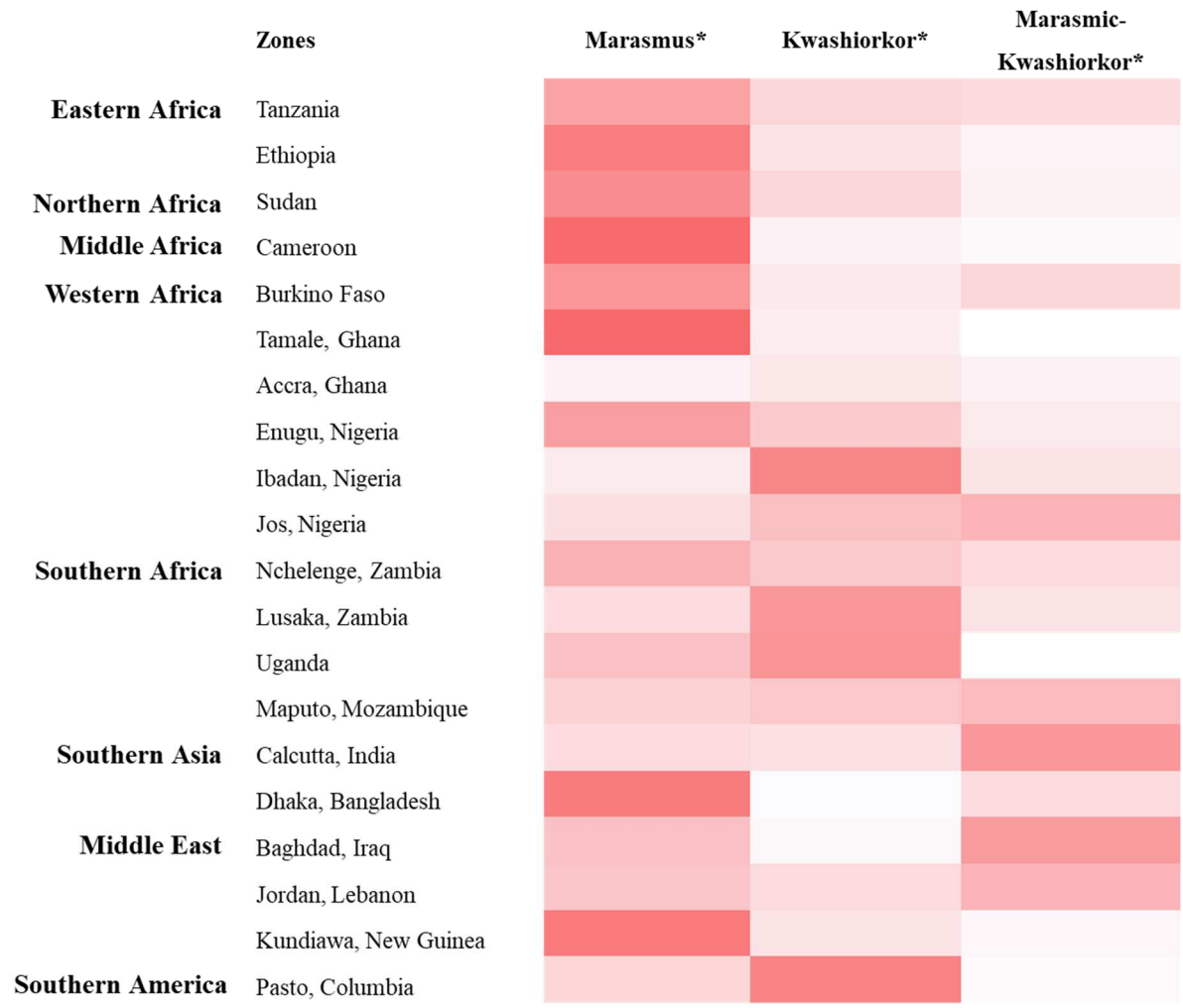
3.1 Difference in Epidemiology

- Incidence and Prevalence:

Kwashiorkor was often the predominant form of protein-energy malnutrition admitted to hospitals in Uganda, Zambia, Nigeria and Columbia (**Figure 2, Suppl. Table S4**). In contrast, marasmus appeared to be the predominant form of severe malnutrition with kwashiorkor representing only a minority of the total admissions in Sudan, Ethiopia, Bangladesh, Burkina Faso and Cameroon (**Figure 2, Suppl. Table S4**). Similarly, community surveys show a much lower relative prevalence for kwashiorkor than marasmus. Rao reported from Southern India that the prevalence of marasmus was twice that of kwashiorkor (10) and Broeck (Democratic Republic of Congo) gave the median prevalence over all survey rounds of 3.2% for marasmus but only 0.2% for kwashiorkor (17). During the early 1970s, a study by Bengoa showed the prevalence in developing countries was 0.2%-1.6% for kwashiorkor and 1.2%-6.8% for marasmus. It is noteworthy that the hospital admissions will be closer to the incidence rate whereas the survey data of Rao, Broeck and Bengoa give prevalence.

Figure 2: Incidence of Kwashiorkor and Marasmus in studies regarding malnourished children admitted to hospital



* Colour intensity was determined by frequencies of Kwashiorkor, Marasmus and Marasmic-kwashiorkor. Accordingly, higher frequencies corresponded to stronger colour.

As noted by Gopalan (18) and Fitzpatrick (19), some communities consistently generate many more cases of kwashiorkor while other nearby communities sharing the same general environment and services do not. They suggested that there were factors that could increase the risk of kwashiorkor or other factors could be protective against kwashiorkor determined geographically. Indeed, later in 1973, Annegers (20,21) conducted a clinical survey and concluded that "frank" kwashiorkor frequently occurred in the zone of low dietary protein-calorie ratios while marasmic children were observed throughout West Africa "regardless of protein levels". Indeed, Raoult's surveys (22) in various countries of West Africa showed that kwashiorkor was most common where the diets were dominated by "root and tuber" or "maize or rice as the staple" such as in the Ivory Coast but kwashiorkor was rare or mild in the Sudan.

In addition, kwashiorkor tended to be more common in the rainy season (23,24). Lindtjørn reported that marasmus was the most common form of acute malnutrition in most areas of Ethiopia, whereas two areas, Kambata-Hadiya and Wolayta (known to have humid and temperate climate), had a high kwashiorkor prevalence rate (24). Aflatoxins (produced by *Aspergillus spp.*), which are particularly prevalent in areas of high relative humidity (25), were consistently detected in the liver and increased in the plasma of children with kwashiorkor (**Grade A - Figure 3-4**). However, the difference in damage caused by aflatoxin in kwashiorkor and marasmus is likely to be related to the glutathione depletion in kwashiorkor (26). Conversely, there are areas where aflatoxin is not found in children with kwashiorkor (27).

Overall, diets, geographical locations, climate and aflatoxin exposure appeared to be key factors affection the ratio between the prevalence of kwashiorkor and marasmus.

212 **Figure 3: Specific characteristics in Kwashiorkor (Grade A and B)**

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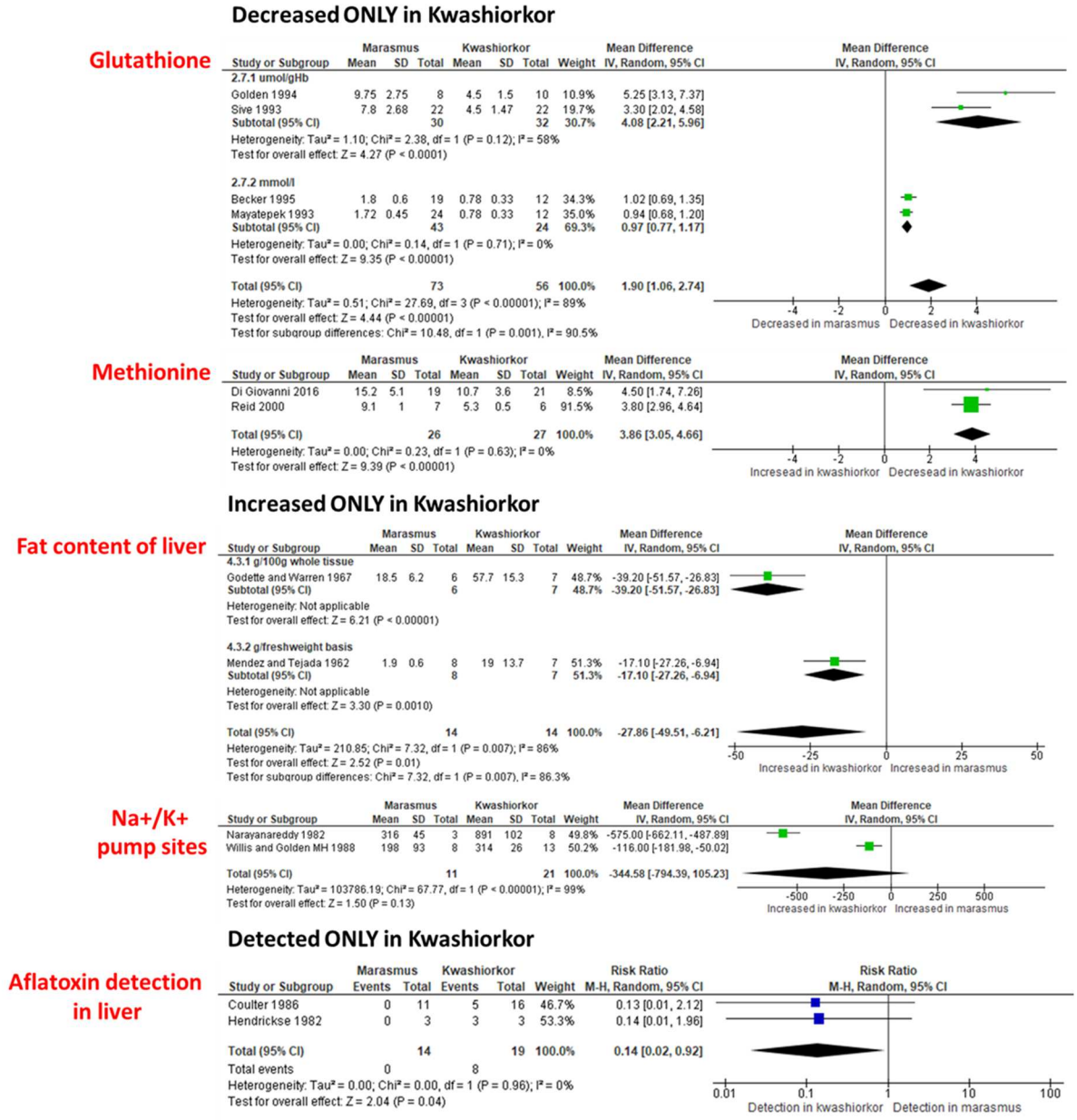
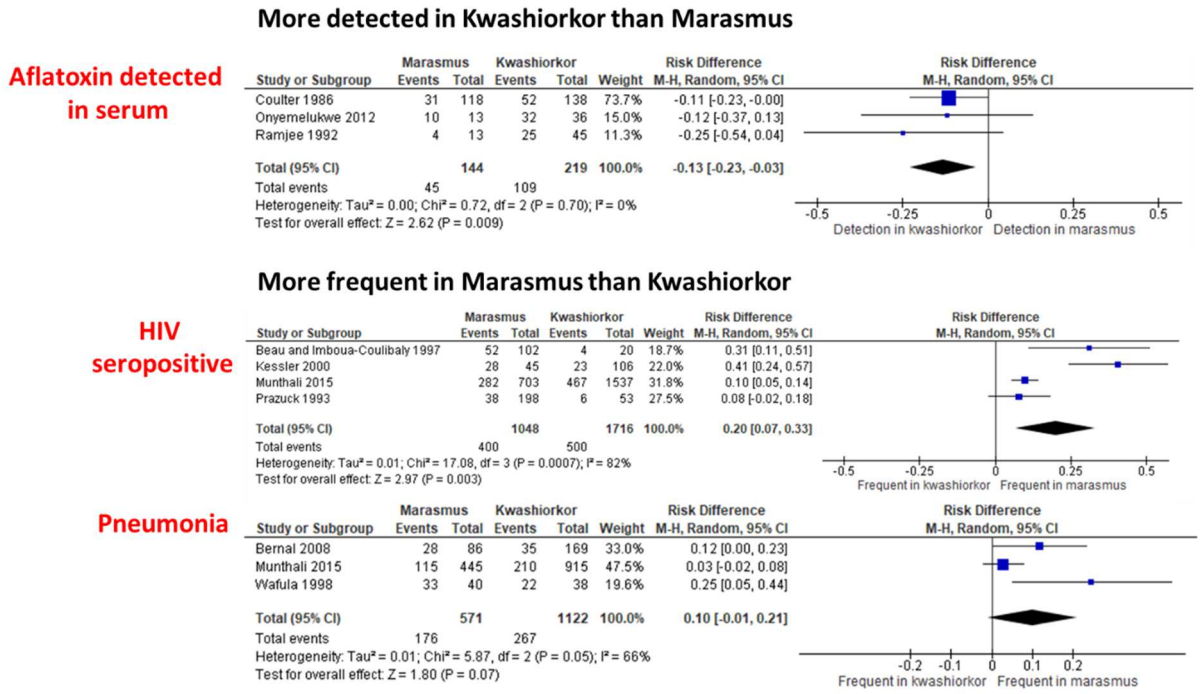


Figure 4: Difference in co-morbidity confirmed by meta-analysis between Kwashiorkor and Marasmus (Grade A and B, non-specific)



- Mortality:

In 1958, Béhar's findings demonstrated that kwashiorkor was a significant cause of death in 4 highland villages of Guatemala with a mortality rate of 20 per 1000 individuals and 58% of cases occurred in children under the five years of ages (28). Indeed, most studies reported that mortality occurred more frequently in oedematous malnutrition than in non-oedematous malnutrition, regardless of a geographic factor (**Table 2**). The mortality from severe malnutrition was up to 40% for many years (29); this has been ascribed to an incorrect understanding of the pathophysiology and consequent incorrect treatment. It has recently fallen to lower levels, with kwashiorkor having about twice the mortality of marasmus; children with both conditions have a very high mortality rate (30).

- Co-morbidity and Infection:

WHO experts confirmed that severe malnutrition generally had a synergistic interaction with infection (31). Infections are very common in malnourished children; the most common were gastro-enteritis, septicaemia, bronchopneumonia, tuberculosis and intestinal parasites. In 1958, Béhar through his investigation into the causes of death of children in 4 rural communities in Guatemala demonstrated the correlations between malnutrition, diarrhoea and other infectious diseases: diarrhoea was presented in 98% of the cases and bronchopneumonia in 70% of the cases (28). He suggested that infection initiated and precipitated the stress that leads to the development of kwashiorkor in many cases. One year later, Scrimshaw noted that kwashiorkor often occurred in children just after an acute infection, most commonly diarrhoea or measles (32,33). This did not apply to all infections; they showed that intestinal parasites which were usually considered as an additional stress factor in the pathogenesis of kwashiorkor, were as common in children of the same age without kwashiorkor as in those with kwashiorkor (32,33). Through the 1960s and 1970s, from a study in Santa Maria de Cauqué (a Guatemalan village), Mata determined that

gastrointestinal infection was a major factor that damaged intestinal mucosa thus causing malabsorption; he concluded that infection played a major part in the development of malnutrition (34). Marasmus was the predominant form of malnutrition amongst HIV infected children; it was consistently reported in many studies and confirmed by our meta-analysis **(Grade A- Figure 4)**. Bacteraemia (**Grade C**) was reported to be 3.5 times more common in kwashiorkor than marasmus in a hospital study by Friedland in South Africa most frequently due to gram-negative enteric microorganisms (35). The proportion of deaths due to bacteraemia was much higher in kwashiorkor than marasmus, 25% and 2%, respectively (35). Meanwhile overall mortality rate in the 2 groups was similar, 13% for kwashiorkor and 15% for marasmus (35).

These results show a marked difference between marasmus and kwashiorkor and also show a good correlation of the 2 diseases with their clinical characteristics. Marasmus is a more chronic illness, characteristics of a deprivation syndrome and appears to be the most prevalent type of severe acute malnutrition (SAM) in many regions and is most frequent in those with HIV infection. Kwashiorkor in typical cases is an acute disease which is usually precipitated by infection (diarrhoea, measles) and complicated by septicaemia and frequently fatal bacteraemia.

3.2. Difference in Nutrition

The prevailing concept of the aetiology of marasmus and kwashiorkor from the onset of the investigation by the United Nations was that marasmus resulted from a lack of energy from foodstuffs, severe long-term food deprivation or very early weaning, whereas kwashiorkor was associated with improper weaning and a diet deficient in protein. These views were officially endorsed in the 3rd report of FAO and WHO (8) which stated that marasmus occurs after prolonged carbohydrate and fat deprivation (in addition to protein deprivation) whereas kwashiorkor is characterized by inadequate protein intake. Then, in

1962, the 6th report of FAO/WHO (11) designated kwashiorkor and marasmus and intermediate stages (marasmic-kwashiorkor) as "protein-calorie deficiency diseases". From that moment on, kwashiorkor was defined as one form of severe malnutrition which is related diet with severe deficiency in protein (or good-quality protein) relative to energy. In contrast, marasmus is related to a balanced deficiency of protein and calories or inadequate amounts of good-quality diet (36). This was first challenged by Gopalan when he looked at the diets of children with kwashiorkor and marasmus in India and found no qualitative or quantitative differences in the diets of the two groups of children, suggesting an additional non-dietary factor at play in kwashiorkor (18).

More recently, this early observation has been confirmed in terms of protein and energy, however differences were found. Sullivan in 2006 reported that eggs and tomatoes (important source of antioxidant micronutrients, including vitamin C, lycopene and carotenoids) were consumed less frequently by children with kwashiorkor than those with marasmus (37). Next, Kismul in 2014 showed that children with kwashiorkor consume fewer sweet potatoes and papaya which are characterized by a high β-carotene content (38). The reports of Sullivan and Kismul stressed the importance of antioxidant foods and suggested a possible aetiological association between antioxidant consumption and kwashiorkor. Thus, empirical dietary evidence that children with kwashiorkor have a specific decrease in total protein intake as the basis of their illness has not been confirmed.

Since the Biafran war, milk has been the mainstay of the nutritional treatment of malnutrition. A study by Brewster showed that, despite the similar densities in protein and energy, maize based diets were inferior to milk. Maize based diets appeared to be associated with a defect of intestinal mucosal barrier function whereas one of the beneficial effects of milk was an improvement of intestinal permeability (39). Kwashiorkor children had a lower mortality with the milk-based diet compared with a maize-based diet (39). Despite the

evidence that milk-based diets had been used successfully for rehabilitation for many years, there was a political problem due to consideration that lactose intolerance and cows' milk allergy might affect the treatment of predominantly black children in the developing world. This was based upon a consideration in the USA that black children were intolerant to milk whereas white children are tolerant; consequently, this led to cow's milk allergen avoidance and replacement by a nutritionally deficient diets (such as Rice Dream milk™, goat's milk, sugared soft drink) (40-42). Due to this consideration, some kwashiorkor cases were reported in rich developed countries as a consequence of unorthodox diets and nutritional ignorance of well-intending but misinformed parents; examples are unnecessarily restrictive diets based on a principle of exclusion during illness like the "fruitarian" diet (4,43,44). As a consequence, some restrictive diets are leading increasingly iatrogenic nutritional issues. Indeed, both marasmus and kwashiorkor have been mentioned in several reports as the results of medical mismanagement leading to negligent adverse events (45,46). These reports emphasized the potential danger of inappropriate restrictive diets in infants and stressed the need for careful nutritional guidance in the management of nutritional diseases (42).

Overall, the only difference in dietary nutrient intake between kwashiorkor and marasmus confirmed with reliable data is the inadequate high-antioxidant food consumption by kwashiorkor patients; this taken together with the change in plasma antioxidant levels (which we will discuss later in "Difference in Biologic features") appear to be a potential discriminant characteristic of kwashiorkor from marasmus.

3.3. Difference in Clinical features

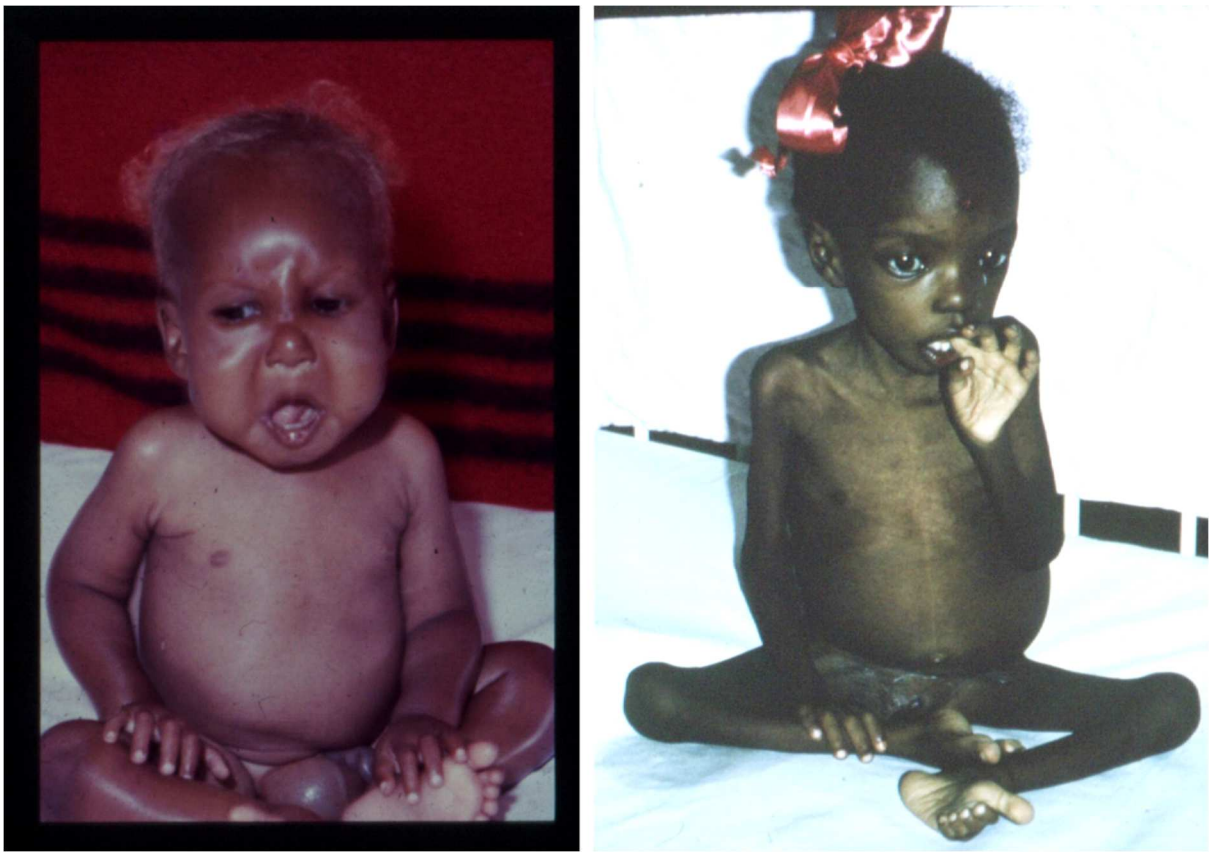
In 1933, Dr. Williams described kwashiorkor as a well-marked syndrome with the presence of oedema, particularly of the hands and feet, followed by wasting, diarrhoea, irritability, frequent inflammation of the mucous membranes, variable skin dyspigmentation with skin peeling; these features were described as "constant and unique" (3). The syndrome

occurred in children of either sex, between one and four years old. A “pale, fatty and almost diffluent” liver was found as a special characteristic in children post-mortem (3). Later, Brock and Autret (6) described in detail the clinical features in children with kwashiorkor in West Africa. In their report, they listed 10 clinical characteristics commonly observed in kwashiorkor. The stunting, gastro-intestinal disorders (diarrhoea) and anaemia were common to both kwashiorkor and marasmus. Compared to marasmus, which was characterized by a loss of subcutaneous fat, extreme muscle wasting and atrophy of most organs (47), kwashiorkor differed in the unique features of massive oedema and the specific changes of hair, skin and liver (**Figure 5-6**). The basic skin changes in kwashiorkor were dyspigmentation, with "enamel paint", "flaky paint" or "crazy paving" dermatosis. In contrast, none of the skin changes associated with kwashiorkor is observed in the “typical” infant with marasmus whose skin is dry, wrinkled, and loose, due to marked loss of subcutaneous fat. In marasmus, although the liver and other essential organs are much reduced in size, histological changes are minimal (47), unlike kwashiorkor which is typically characterized by a large fatty liver, fibrosis and dysfunction of several organs (such as pancreatic, renal and mental functions). The mean age at presentation of kwashiorkor children tended to be higher than for marasmus. Kwashiorkor was more associated with bacterial infection, especially bacteraemia and septicaemia whereas marasmus is more associated with HIV infection and rickets. Other signs and symptoms typical of specific vitamin-deficiency syndromes might be found, or not, with a wide variation in clinical characteristics in both kwashiorkor and marasmus.

Following the work of Brock and Autret, Waterlow and Vergara (7) reported their findings of kwashiorkor in Brazil and reported intermediate cases (marasmic-kwashiorkor)**.** As stated by Gopalan in 1968 (18), children with marasmus might develop kwashiorkor and children with kwashiorkor might present the picture of marasmus after shedding their

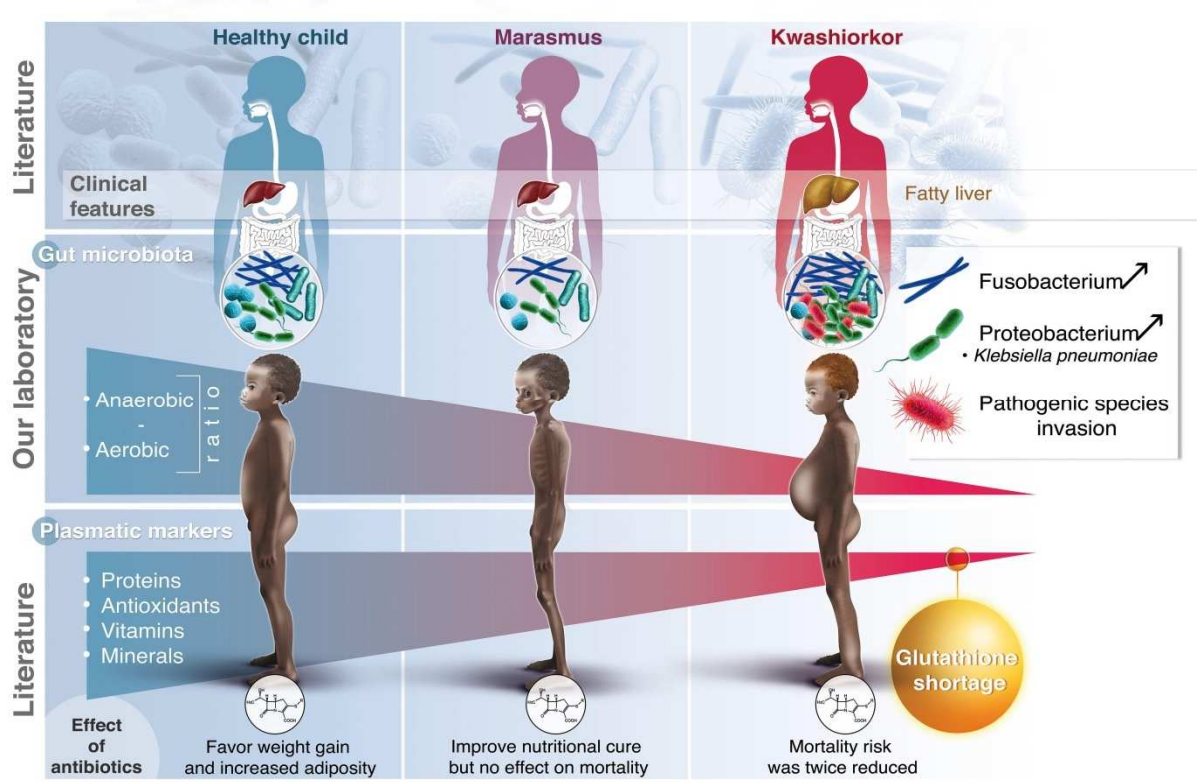
oedema. Clinically, most of the changes in kwashiorkor and marasmus might be present in the mixed form. It has gradually become clear that kwashiorkor and marasmus are different but related and possibly overlapping diseases, with marked differences in their clinical features (**Figure 5-6**).

Figure 5: Difference in clinical features between children suffering from Kwashiorkor (left) and children suffering from Marasmus (right)



Illustrations represent the typical features of most cases of Kwashiorkor and Marasmus: bilateral oedema and depigmented hair in Kwashiorkor; loss of subcutaneous fat and muscle mass in Marasmus. Copyright 2019 by Michael Golden, written consent obtained.

Figure 6: Differential characteristics in Kwashiorkor and Marasmus



366 **3.4. Difference in Biological features**

367 - Free radicals and Antioxidants:

368 One of the earliest studies on the role of free radicals and antioxidants in malnutrition
369 pathogenicity was the study of Golden and Ramdath (48). In the study, they reported that
370 ferritin, a storage form of iron, was particularly high in kwashiorkor whereas the plasmatic
371 vitamin E and zinc concentrations were at a low level; there were especially low levels of
372 antioxidant enzymes such as glutathione peroxidase and very low levels of erythrocyte
373 glutathione (48). The findings effectively initiated the hypothesis that kwashiorkor results
374 from an excess of free radicals and a depletion of antioxidants which opened a new era for
375 malnutrition science. Indeed, several studies have been conducted since, and have confirmed
376 the low level of glutathione observed only in kwashiorkor but not marasmus **(Grade A -**
377 **Figure 3, Table 1**). Furthermore, the decrease in plasma levels of antioxidant proteins
378 (mainly albumin, transferrin and ceruloplasmin), minerals (zinc, copper, selenium) and
379 vitamins (such as vitamin A, C) consistently showed a downward trend from healthy children
380 to marasmus with the lowest levels always observed in kwashiorkor (**Suppl. Table S1-S2**)
381 which was significantly confirmed by our meta-analysis (**Grade A (Grade B for Vitamin C)**
382 **- Figure 7, Suppl. Figure S3**). Importantly, these were associated with a low
383 NADPH/NADP ratio, indicating a change in cellular redox potential towards an oxidisation
384 of the cellular environment (49).

Figure 7: Non-specific characteristics differentiating Kwashiorkor from Marasmus

		Decreased in marasmus	Decreased in kwashiorkor
1. Plasma total protein, albumin, transferrin	Grade A		✓
2. Minerals (Zinc, Copper, Selenium)	Grade A		✓
3. Vitamin A	Grade A		✓
4. Vitamin C	Grade B		✓
5. Plasma phosphate	Grade A		✓
6. Amylase	Grade A		✓
7. Cholesterol, Phospholipids	Grade A		✓
8. Free Fatty Acids	Grade B		✓
9. Insulin, T3 hormone	Grade A		✓
10. T cells count, C3 component, IgA	Grade A		✓
11. IGF-1, Leptin	Grade A	✓	

		Increased in marasmus	Increased in kwashiorkor
1. ALT/AST	Grade A		✓
2. Growth hormone	Grade A		✓

Non-specific characteristics were observed in both kwashiorkor and marasmus but always more pronounced in kwashiorkor (**left**) or marasmus (**right**). Consequently, all non-specific characteristics in Grade A and B (meta-analysis results $p<0.10$ only) were summed up.

On another hand, a high concentration of free circulating iron in children with kwashiorkor has been clearly demonstrated (50) which was not observed in marasmus (51,52). Specifically, a very high level of circulating ferritin observed in kwashiorkor but normal or slightly raised in marasmus (49, 53, 54). The presence of free iron in kwashiorkor was confirmed through iron excretion following deferoxamine administration (55) and measurement of liver iron from kwashiorkor children at autopsy (56,57). These results confirmed that children with kwashiorkor were suffering from significant iron overload which did not occur in marasmus.

- Protein and Amino acids metabolism:

Several studies consistently reported that the depletion in plasma total protein, albumin and transferrin was more pronounced in kwashiorkor than in marasmus; this was confirmed by our meta-analysis (**Grade A - Figure 7, Suppl. Figure S3A**).

In 1998, Manary demonstrated that the rates of whole-body protein breakdown and protein synthesis are slower in children with kwashiorkor than in those with marasmus during acute infection (58).Then, in 2005, Jahoor confirmed this difference and indicated the different responses in protein metabolism to food deprivation between children with and without oedematous malnutrition (59) which suggested that only children with marasmus had the ability to maintain body protein breakdown at the same rate as well-nourished while children with kwashiorkor did not have this capacity.

It was demonstrated that kwashiorkor children have a high disturbance of amino acid metabolism with a consistent and significant reduction of plasma essential amino acids levels with individual amino acids affected to different degrees (60-64). Some non-essential amino acids remained at average levels (62) or might be kept at high level in the plasma of these children (61,63,64). In contrast, there was a particularly marked reduction of cysteine in erythrocytes and methionine in plasma **(Grade A - Figure 3)** and the flux of these amino

acids during whole body protein turnover was compromised. According to Jahoor, in the oedematous children, the low levels of these 2 major sulphur-containing amino acids was associated with slower glutathione synthesis (65). Since there was no difference in the experimental diets given to the oedematous and non-oedematous children, Jahoor stated that the severe shortage of methionine in oedematous children might be the result of a slower rate of whole-body protein breakdown in oedematous children rather than a dietary deficiency (65). Also, in his report, cysteine released from protein breakdown was slower in the oedematous group; however, the amount of cysteine in non-oedematous children was still sufficient to maintain its concentration in plasma and erythrocytes as well as glutathione synthesis rate; this explained why during acute infection oedematous children were unable to maintain glutathione synthesis rate, but non-oedematous children could (65).

- Lipid metabolism:

Increased plasma concentrations of free fatty acids (FFA) were often found in both kwashiorkor and marasmus although the values were consistently higher in kwashiorkor than in marasmic children (**Grade B - Figure 7, Suppl. Figure S3B**). In almost all reports, plasma total cholesterol and phospholipids were consistently and significantly lower in kwashiorkor than marasmus (**Grade A - Figure 7, Suppl. Figure S3B**). Plasma fasting triglycerides are usually low in kwashiorkor (66,67) but not consistently; similarly, cholesterol and phospholipids levels are low, while in marasmus, triglycerides are normal or increased (68,69).

Compared to marasmus, the fatty liver is more intense in kwashiorkor. The high fat content in liver was consistently and significantly reported in kwashiorkor in several studies (**Figure 3, Table 3**). However, the high free fatty acid levels alone couldn't fully explain the fatty liver in kwashiorkor. Lewis suggested that in marasmus, the liver responded to an excessive input of fatty acids by increased production of plasma lipoproteins, whereas in

kwashiorkor the liver was unable to dispose of fatty acids which led to lipid accumulation in the liver (67). This has been associated with mitochondrial and peroxisomal dysfunction and to the lack of peroxisomes that are seen on electron microscopy of kwashiorkor livers (70,71) and confirmed experimentally (72). It is of interest that the liver fat is very slowly mobilised during recovery despite the fact that treatment consists of a very high fat diet (73).

It has been hypothesized that one factor associated with poor prognosis in kwashiorkor, but not in marasmus, is impaired lipid catabolism, which limits the supply of energy that is essential for survival when dietary intake is inadequate. In keeping with the hepatic studies, Badaloo suggested inefficient mobilization and utilization of lipid for energy in kwashiorkor but not in marasmus was due to a less efficient fat break down and fatty acids oxidation in kwashiorkor using stable isotope tracer dynamic studies (74). It has been demonstrated that the level of plasma carnitine was significantly lower in children with kwashiorkor (61,75). Thereby, decreased fatty acid transported by carnitine across the inner mitochondrial membrane for β-oxidation could be another factor contributing to slower lipid oxidation in children with kwashiorkor (74).

- Endocrine changes:

In general, fasting glucose is in the low-normal range accompanied by a low fasting serum insulin level; this occurs in both kwashiorkor and marasmus without a clear difference between the groups (**Grade A - Figure 7, Suppl. Figure S3E, Suppl. Table S1-S2**). Becker showed an impaired insulin response in most children with kwashiorkor and some children with marasmus (76) and suggested that impairment in glucose tolerance in kwashiorkor might be related to disturbed insulin secretion. Indeed, endogenous glucose production (EGP) which is an important determinant of glucose tolerance, was demonstrated to be decreased in kwashiorkor compared with marasmus (**Grade A - Figure 7, Suppl. Figure S3E, Suppl. Table S1-S2**).

Growth hormone was inconsistently raised in both kwashiorkor and marasmus; but in most studies, the mean values were significantly higher in kwashiorkor than in marasmus (**Grade A** - **Figure 7, Suppl. Table S1-S2, Suppl. Figure S3E**). The loss of adipose tissue was found to be more prominent in marasmus compared with kwashiorkor, and this is consistent with reduced levels of leptin and IGF-1 (insulin-like growth factor-1) (**Grade A** - **Figure 7, Suppl. Table S1-S2, Suppl. Figure S3E**).

Furthermore, thyroid hormones T3 and T4 levels were consistently lower and TSH levels were higher in kwashiorkor compared to marasmus (**Grade A, B and B, respectively - Figure 7, Suppl. Table S1-S2, Suppl. Figure S3E**), which appeared to be a result of depressed thyroid function.

- Electrolyte metabolism:

Vajreswari showed marked alterations in the erythrocyte's membrane (EM) in kwashiorkor children, while marasmic children were similar to normal children (77). These altered membrane properties included reduced membrane fragility, increased membrane sodium, increased Na+/K+ pump sites (sodium pump) and increased membrane Na+/K+-adenosine triphosphatase (ATPase) activity (77). Particularly, the number of Na+/K+ pump sites per erythrocyte was consistently increased in kwashiorkor but normal in marasmus, (**Grade B** - **Figure 3, Suppl. Table S1-S2**). In accordance with altered erythrocyte membrane Na+/K+-ATPase the activity of the sodium pump is increased in kwashiorkor but decreased or normal in marasmus (78). The results suggested that the major changes in membrane Na+/K+-ATPase were not critical in the pathophysiology of marasmus. Intracellular sodium is high in both kwashiorkor and marasmus; however, this is due to quite different mechanisms. In marasmus this is due to slowing of the sodium pump with decreased sodium efflux whereas the membrane is leaky in kwashiorkor with increased sodium efflux (79); the leak in the membranes can be reproduced experimentally in erythrocytes by

depleting them in glutathione to the levels found in kwashiorkor (80) which implicates oxidative stress in the genesis of the electrolytic abnormalities in kwashiorkor.

- Inflammatory responses:

In 2010, Velasquez showed that children with kwashiorkor had significantly higher concentrations of IL-1 β, IL-6, IL-8, IL-10, and TNF-α in comparison to those with marasmus and suggested that these pro-inflammatory cytokines could be critical biomarkers during infectious process of kwashiorkor (81). By meta-analysis, IL-6 level was consistently higher in the kwashiorkor than in marasmus (**Grade B** - **Suppl. Table S1-S2, Suppl. Figure S3F**). Manary demonstrated that marasmus was associated with an attenuated acute-phase response but not a diminished cytokine response to acute infection, since infected marasmic children had a lower level of acute-phase proteins (CRP) when compared with well-nourished infected children, but the serum cytokine concentrations remained higher (82). The author suggested that acute-phase responses to acute infection are "blunted" in marasmus. Collectively, the available information suggests that the ability to sustain high serum levels of pro-inflammatory cytokines appeared to be maintained in both kwashiorkor and marasmic children. Furthermore, serum concentrations of IgM, IgG and IgA were generally unaffected or modestly increased in severe malnutrition (83).

- Liver and pancreas function:

In 1948, Waterlow (56), in his study in British West Indian infants, demonstrated fatty infiltration of the liver in oedematous malnutrition for the first time. In contrast, no cells showed fatty change in marasmus (84). Overloading the hepatocytes with fatty acids and the depletion of carnitine suggests that impaired mitochondrial fatty oxidation namely impaired β-oxidation specifically occurs in kwashiorkor. Liver dysfunction in kwashiorkor was also obvious with impaired plasma protein synthesis and export (such as depletion in plasma total protein, albumin, transferrin) and toxic damage to the cells (including increased hepatic iron,

produced lipid peroxidation) and by noxious exposures to toxins such as the aflatoxins and aflatoxicol which were not detected in plasma and less frequently in the livers of children with marasmus (85,86).

On another hand, histological studies showed that pancreatic fibrosis and pancreatic acinar atrophy were constant features among children with kwashiorkor, but this is also found in children with marasmus, as a non-regular feature (87,88). Like the histological changes, the diminution of serum amylase and lipase are greater in children with kwashiorkor than in those with marasmus (**Grade A and B, respectively - Figure 7, Supp. Table S1-S2, Figure S3B**). These pancreatic abnormalities and the high levels of classical markers of hepatic damage, serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST), indicate that both the pancreas and the liver are functionally damaged as a characteristic feature of kwashiorkor; these features are much lower or absent in marasmus in most studies.

Overall, it is obvious that fatty liver is a dominant feature of kwashiorkor while this feature is much less present in marasmus (73). Depletion in glutathione, serum methionine shortage, excessive free circulating iron with the increase in Na+/K+ pump sites and cell membrane damage appear to be potentially specific features which can distinguish kwashiorkor from marasmus (**Figure 3, Table 1**).

3.5. Difference in Gut microbiota

- Commensal gut microbiota:

In 2013, Gordon suggested a direct link between kwashiorkor and gut microbiota since this phenotype could be transmitted to gnotobiotic mice through faecal microbiota transplantation (89). According to recent studies by Tidjani Alou *et al* (90) and Pham *et al* (91), both kwashiorkor and marasmus are characterized by an altered gut microbiota.

Comparing the gut microbiota composition of children with kwashiorkor and marasmus, there was a decrease in total species diversity; in particular there was a

predominant loss of anaerobic species in both kwashiorkor and marasmus, but this was always more pronounced in kwashiorkor than in marasmus (91). To our knowledge, only this study compared the gut microbiota of children with marasmus and kwashiorkor. Pham suggested that the gut microbiota status reflects the nutritional status of children with SAM; children with marasmus consistently held an intermediate place between control children and kwashiorkor patients. This is consistent with previous findings on metabolism (**Figure 3; Suppl. Table S1-S2**). Also, in the study, the clustering analysis showed that there was a microbiota specific to each form of malnutrition without being altered by age, sex or geographic origin confirming the microbiome as a difference between kwashiorkor and marasmus (91). Furthermore, there was a specific difference at phylum level between kwashiorkor and marasmus. An increase in the proportion of *Proteobacteria* and *Fusobacteria* was only observed in kwashiorkor whereas a decrease in the *Bacteroidetes* proportion occurred only in marasmus, as presented in **Figure 6** (91). For the first time, these findings pointed to another potential specific feature to distinguish kwashiorkor and marasmus based on gut microbiota composition.

From our meta-analysis, Aflatoxin (mainly produced by *Aspergillus spp*.) appeared to be specific for kwashiorkor since it was consistently and significantly detected in livers of children with kwashiorkor only (**Figure 3**). From our knowledge, *Aspergillus* and *Candida*, were two of the most recurrent and/or dominant fungal genera inhabiting the human gut, according to metagenomic analysis (92). Future studies focusing on the fungal community should explore the link between these components of the gut microbiota and malnutrition.

- Proliferation of pathogenic species:

Previously, bacterial overgrowth in the small intestine has been consistently reported in children with malnutrition in the study by Mata in 1972 (34). The only difference noted was that children with severe malnutrition showed more *Enterobacteriaceae* in the small

intestine and an altered faecal flora, qualitatively and quantitatively (34). Later, Scragg and Appelbaum showed that the majority of pathogens isolated from blood cultures of malnourished children were Gram-negative (including *Salmonella, Escherichia coli, Enterobacter cloacae, Pseudomonas aeruginosa* and *Klebsiella pneumoniae*) (93). Particularly, 5 of the 8 children from whose blood salmonellae were isolated had the same type of organism in their stool, suggested a breach in the intestinal barrier in malnourished children (93).

Recently, Pham demonstrated that the proliferation of several potentially pathogenic species was observed specifically in kwashiorkor; these included *Klebsiella oxytoca, Klebsiella pneumoniae, Hafnia alvei, Salmonella enterica, Gemella haemolysans, Enterobacter cloacae, Escherichia coli* and *Acinetobacter baumanii* (91). In contrast, none of the bacterial species enriched in marasmus were recognised pathogens (91). Of the 8 potentially pathogenic species which were only enriched in the kwashiorkor cases 7 were Gram-negative bacteria whose outer membrane contains lipopolysaccharides (LPS) or endotoxins. The presence of intestinally derived LPS in circulating blood (endotoxemia), particularly at the host-pathogen interface, is considered an important factor in the development of alcoholic hepatitis (94). Recently, Yuan and colleagues reported a high blood alcohol concentration in a NAFLD patient (non-alcoholic fatty liver disease) consuming an alcohol-free, high-carbohydrate diet and demonstrated that certain strains of *Enterobacteriaceae,* especially *Klebsiella pneumoniae* produce high levels of alcohol which could be responsible for the liver pathology (95). Non-alcoholic steatohepatitis (NASH) is associated with proliferation of *Proteobacteria*. It is possible that a similar mechanism occurs in kwashiorkor so that particular gut microbiota bacterial or fungal strains, especially *Klebsiella pneumoniae,* may contribute to the pathogenesis of the liver disease in kwashiorkor through ethanol production in an oxidized (aerobic) atmosphere (96). Moreover,

603 *Escherichia coli* and *Enterobacter cloacae* are bacterial species associated with endotoxin-
604 related obesity and insulin resistance (97,98).

605 Our recent findings in gut microbiota which add to the distinction between
606 kwashiorkor and marasmus have to be reconciled with the known distinctive
607 pathophysiological differences and the place of the microbial changes in the aetiology of
608 kwashiorkor. In particular gram-negative bacteria, especially *Klebsiella pneumoniae* and
609 endotoxemia, in kwashiorkor may contribute to a better understanding of: i) the manifestation
610 of Gram-negative infection in malnourished people; ii) the instrumental role of the intestinal
611 microbiota on the development of obesity (one of the long-term consequences of SAM) in
612 recovered malnourished people; iii) a possible similar process in kwashiorkor pathogenesis
613 and in alcoholic and non-alcoholic fatty liver diseases (NAFLD). This would allow us to
614 initially establish a specific process related to the intestinal microbiota in children affected by
615 kwashiorkor, but also to develop more accurate prognostic evaluation and more effective
616 treatments for severe acute malnutrition.

617 **3.6. Difference in Genetics**

618 In 1968, Gopalan stated that marasmus and kwashiorkor could coexist in the same
619 community where the dietary pattern of the children who developed kwashiorkor or
620 marasmus was not qualitatively different (18). He suggested a potential genetic predisposition
621 might be responsible for the development of kwashiorkor and marasmus in the community. In
622 twin studies of children from rural villages in Malawi (89), during their first 3 years of life,
623 43% of children became discordant for malnutrition with only 7% being concordant for the
624 type of acute malnutrition. Smith didn't find any significant difference between concordance
625 for acute malnutrition and zygosity, neither was there a difference in the number of
626 monozygotic versus dizygotic twin pairs affected with malnutrition, nor a difference in the
627 incidence of discordance for kwashiorkor or marasmus for zygosity (89).

After receiving treatment with ready-to-use therapeutic food (RUTF), the gut microbiomes of the healthy co-twins followed the progression of development towards normal older children's microbiota, but the microbiome of their siblings with the kwashiorkor failed to mature (89). Forrester has demonstrated that children who developed marasmus had much lower birth weights than those who developed kwashiorkor and suggested that marasmus was associated with a greater prenatal disadvantage, especially a more restricted in-utero nutritional environment (99). Hanson and Gluckman argued that the foetal response to poor nutrition would induce epigenetic and physiological changes in the children after weaning (100). There are distinct differences in epigenetic imprinting of the genome of children with marasmus and kwashiorkor that persist to adulthood. This finding indicates a "persistent developmentally induced phenomena" mediated by epigenetic processes which may influence the infant's response to acute malnutrition (101). How such epigenetic changes influence the gut microbiota has not been explored to our knowledge.

3.7. Difference in response to Antibiotic Treatment

Since acute bacterial infection is common and serious in severe malnutrition, antibiotics have long been recommended in the treatment of all cases of kwashiorkor and marasmus. But the most suitable antibiotic regimens remained to be discussed: Penicillin was widely used, sometimes with gentamicin, streptomycin or more recently with cephalosporin. There is a proliferation of many *Enterobacteriaceae* species in kwashiorkor, such as *Escherichia coli, Klebsiella oxytoca, Klebsiella pneumoniae* and *Hafniaceae,* including *Hafnia alvei* (91). These species are able to produce β-lactamase to resist penicillin suggesting that penicillin may be suboptimal for the management of kwashiorkor (91). Indeed, Trehan has demonstrated that children receiving cefdinir (a third-generation cephalosporin) had a higher nutritional recovery rate and lower mortality rate than those who received amoxicillin (102). As reported above, endotoxins might be involved in the "similar"

653 pathogenesis of kwashiorkor and NAFLD. Thus, antibiotics with better efficiency against
654 *Enterobacteriaceae* such as cephalosporin or rifaximin emerge as a potential option in
655 antibiotic treatment for kwashiorkor (103).

656 Particularly, our meta-analysis of studies analysing the treatment with antibiotics in
657 malnourished children showed that antibiotics had a different effect on mortality rate in
658 children with or without kwashiorkor (**Grade A - Figure 8A**). Antibiotics (amoxicillin and
659 cefdinir) reduced mortality in children with kwashiorkor and marasmic-kwashiorkor (OR
660 0.48 - 0.55, $p < 0.05$) but did not reduce mortality in children with marasmus (OR 0.98, $p = 0.95$).
661 Furthermore, there was no significant difference in the magnitude of the antibiotic's
662 effect between children with marasmic-kwashiorkor and kwashiorkor ($p = 0.7$). Based on the
663 number need to treat (NNT) calculation, the meta-analysis indicated that to save 1 additional
664 child with marasmic-kwashiorkor, 11 children must be treated (ratio 1/ARR (absolute risk
665 reduction) = 1/0.09). Similarly, to save 1 child with kwashiorkor, 33 children must be treated
666 (1/ARR = 1/0.03). But antibiotics did not save any child with marasmus. The difference
667 between the subgroups was highly significant ($p = 0.0006$).

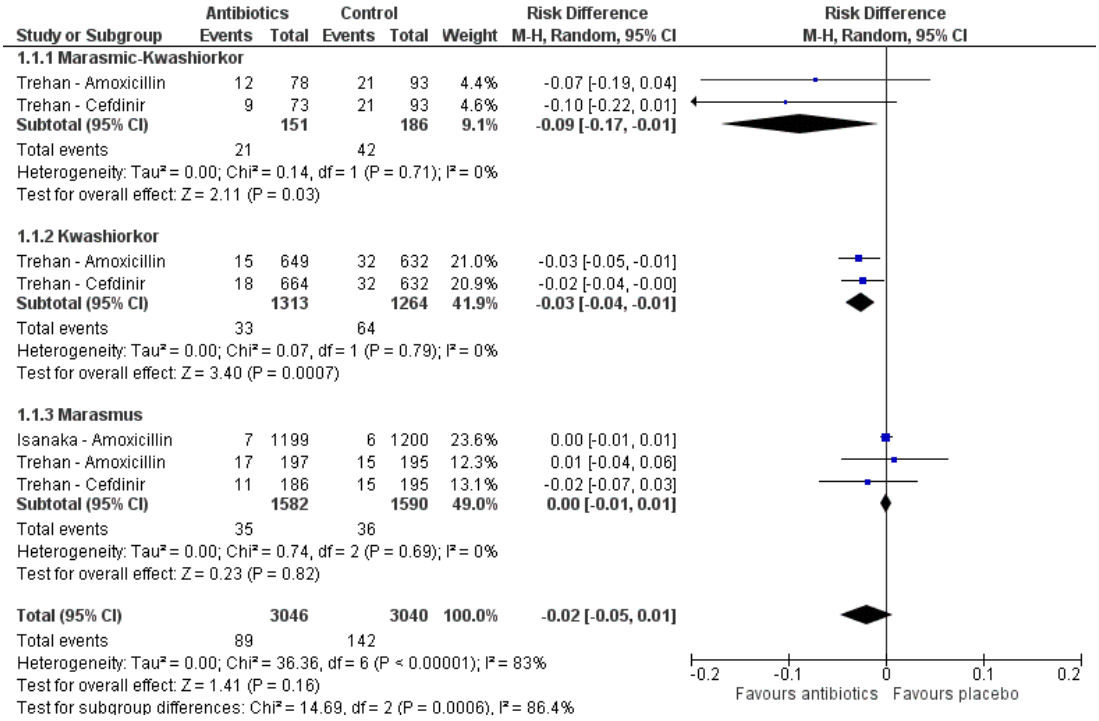
668 Strikingly, Friedland compared mortality associated with bacteraemia in 792 children
669 with severe acute malnutrition (35). By re-analysing their study data, we have confirmed that
670 1 in 4 deaths in the kwashiorkor group was associated with bacteraemia whereas no deaths
671 were associated with bacteraemia in the marasmic group; the attributable fraction in the
672 population was 25% (CI: 15.5 - 32.5) in the oedematous group (kwashiorkor plus marasmic
673 kwashiorkor) versus 2.3% (CI: 2.6 to 7.3) in the non-oedematous/marasmic group. Taken
674 together with the difference in the effect of antibiotics on survival, this suggests that
675 dysbiosis, invasion and bacterial translocation play a major role in the pathogenic process in
676 children with kwashiorkor but has much less effect in children with marasmus. At least 69%
677 of the bacteria isolated in the blood cultures of these children were not sensitive to

678 amoxicillin and only ceftazidime was effective on 100% of the bacteria (35). Both Trehan
679 and Isanaka confirmed that children with severe acute malnutrition significantly gained more
680 weight and recovered more quickly when they received antibiotics. Our meta-analysis
681 showed that antibiotics were significantly and consistently effective for the nutritional
682 recovery of all 3 forms of SAM (marasmic-kwashiorkor, kwashiorkor and marasmus) without
683 a significant difference between groups (**Grade A - Figure 8B**).

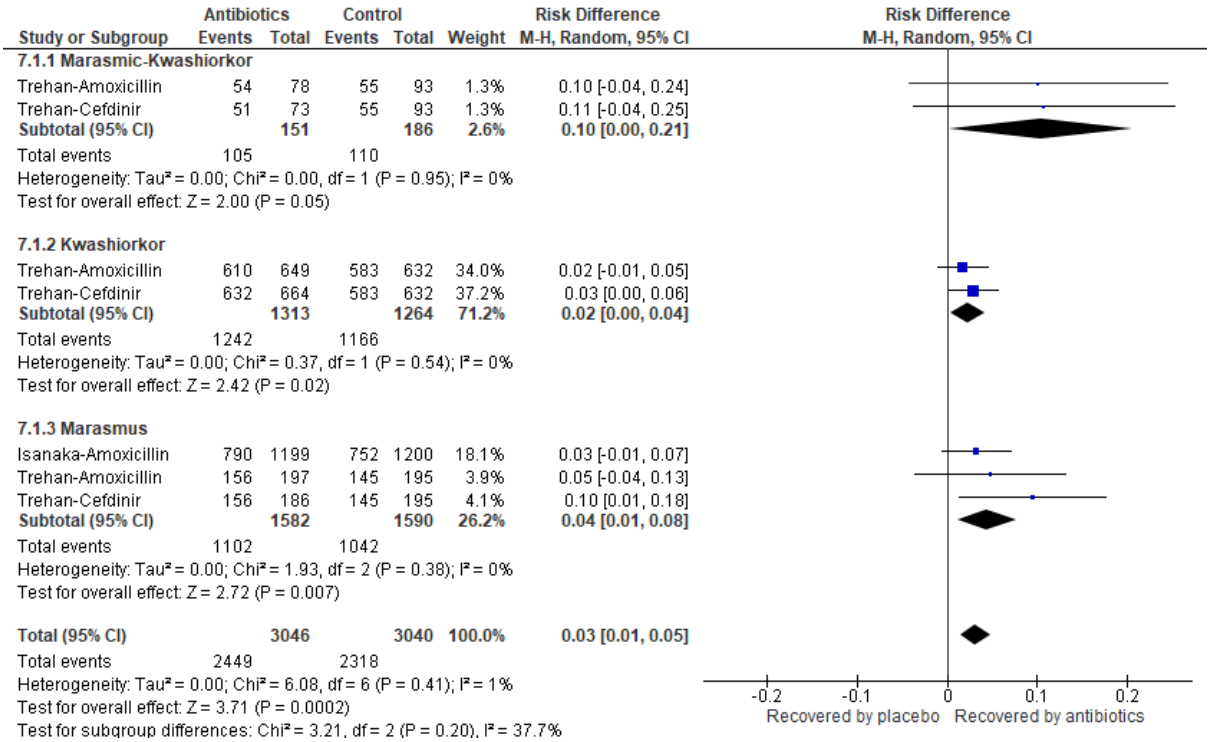
684 Overall, the very marked difference in antibiotic treatment on survival of kwashiorkor
685 and marasmic patients was consistent with the proliferation of pathogenic species in
686 kwashiorkor that were not prevalent in marasmic children. This might be important for the
687 specific management of each type of severe malnutrition and promotes more effective
688 treatment and prognosis at least for kwashiorkor. Rationalisation of antibiotic policy in
689 protocols for treating malnutrition is important to reduce mortality, improve recovery and
690 reduce the emergence of resistant pathogens.

Figure 8: Meta-analysis of studies analyzing the treatment with antibiotics in malnourished children

A- Effect on mortality rate



B- Effect on nutritional recovery



3.8. Difference in Prognosis

The use of updated protocols based upon the pathophysiological studies and the invention of ready-to-use therapeutic foods (RUTF) have successfully reduced mortality in children with severe acute malnutrition (SAM) to “acceptable” levels. However, there is also incomplete restoration to normality, continuing growth retardation (or stunting) and persistent dysbiotic gut microbiota. There may also be long-term consequences such as increased risk of developing metabolic syndrome as adults, but this remains to be investigated.

It has been reported that although cases of oedematous malnutrition have a higher mortality and more complications than marasmic children, they recover more rapidly than severely wasted children post-admission (104). According to Galler, the effect of previous marasmus on adolescent’s growth appeared to be more severe, greater in girls than in boys especially in sexual maturation; in contrast in kwashiorkor, neither boys nor girls had deficits in physical growth or sexual maturation (105). Additionally, intellectual performance was found to be impaired in both kwashiorkor and marasmus whereas the persistent deficits in fine motor skills was more extensive in children with histories of kwashiorkor than those of marasmus (106).

4. Conclusions

Severe acute malnutrition is a complex mixture of a number of nutritional conditions that are difficult to disentangle and are still incompletely understood. They are often complicated by various degrees of deficiencies in vitamins and trace minerals that are not normally assessed clinically. This review is not intended to demonstrate the pathogenetic factors of malnutrition, but rather to adopt a systematic arrangement of available information to present a descriptive picture of the differences between kwashiorkor and marasmus (**Figure 6, Table 3, Suppl. Table S2**). Oedema, fatty liver and skin depigmentation are characteristics of kwashiorkor which are much less frequent in marasmus, however in

practice there are many patients exhibiting features of both conditions, when they are termed as having “marasmic-kwashiorkor”.

The depletion in glutathione, serum methionine shortage, an excessive level of free circulating iron and the increase in Na+/K+ pump sites appear to be specific features which can distinguish kwashiorkor and rarely occur in marasmus. Some characteristics, such as a decrease in plasma levels of antioxidant proteins (mainly albumin, transferrin and ceruloplasmin), minerals (zinc, copper, selenium) and vitamins (such as vitamin A, C) consistently showed a lower levels in marasmus than occur in healthy children but the levels in kwashiorkor are much lower than in marasmus; this difference was significant by meta-analysis. These changes are consistent with the depletion of anaerobic species in the gut microbiota of malnourished children and are compatible with the oxidative stress which characterises kwashiorkor. In contrast, other characteristics related to body fat mass and poor growth including a decrease in serum leptin and IGF-1 levels are consistently more pronounced in marasmus than kwashiorkor. This is consistent with marasmus being associated with a restricted dietary lacking in type II nutrients (107) with an appropriate adaptive response and a loss of muscle and adipose tissue.

Consistent findings of our review suggest that dysbiosis, invasion and bacterial translocation play a major role in the pathogenic process in children with kwashiorkor but to a lesser extent in children with marasmus. Indeed, we only observed enrichment of pathogenic bacteria in the gut of children with kwashiorkor; bacteraemia was responsible for a quarter of deaths in children with a kwashiorkor but no deaths in those with a marasmus in Friedland’s study, and antibiotics improved survival only in children with a kwashiorkor in the studies available for meta-analysis. These results should lead to the early administration of broad-spectrum antibiotics effective on *Proteobacteria*, particularly *Klebsiella pneumoniae* (35) in children with kwashiorkor. However, this should not lead to the

748 discontinuation of the recommended amoxicillin for any child with severe acute malnutrition
749 as this treatment is associated with improved nutritional cure in all forms of malnutrition
750 (marasmus, kwashiorkor and kwashiorkor marasmus).

751 The reasons for the difference in bacterial invasion and colonisation in kwashiorkor
752 compared to marasmus need to be established. In kwashiorkor there is a specific reduction in
753 cell surface glycosaminoglycans which form the attachment molecules for many bacteria (for
754 example kwashiorkor children do not get Cholera) (108). The particular reduction in
755 anaerobic species in kwashiorkor may be related to their general oxidised redox of the cells
756 and intestinal contents (49,91,109). Such differences in the intestinal and somatic
757 environment in kwashiorkor may change the spectrum of organisms suited to colonise and
758 infect.

759 The result needs to be confirmed in different geographic situations and patient
760 populations and be related to measures of the disease severity. This is because some of the
761 data are derived from children treated as out-patients that are not critically ill and have a
762 reasonable appetite; nevertheless, the finding is potentially important for the specific
763 management of each type of severe malnutrition that will promote more effective treatment
764 and improve the prognosis for severe malnutrition.

765 Finally, similar characteristics found in kwashiorkor and NAFLD (proliferation of
766 *Proteobacteria*, especially *Klebsiella pneumoniae* which is specifically able to produce
767 ethanol) which suggests a possible similar pathological process in the pathogenesis of
768 kwashiorkor and non-alcoholic steatohepatitis. Such understanding may allow us to formulate
769 treatments that specifically modify the intestinal microbiota of children affected by
770 kwashiorkor and re-establish the compliment of anaerobes and suppress the pathogenic
771 species.

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Table 1: Potential specific characteristics for Kwashiorkor or Marasmus

Characteristics	Kwashiorkor	Marasmus	Confirmed by meta-analysis*
Clinical features			
Oedema	+++		
Depigmentation skin, flag sins, flaky paint, crazy paving	+		
Loss of subcutaneous fat		+	
Dry skin, wrinkled, and loose		+	
Liver			
Enlarged liver	+		
Fatty liver	+		A
Aflatoxin detected in liver	+		A
Biological markers (activity in serum or plasma)			
Glutathione	↓		A
Methionine (Sulfur-containing amino acid)	↓		A
Free circulating iron	↑		C
Na+/K+ pump sites	↑		B
Gut microbiota			
Pathogenic species proliferation	+		C
Proteobacteria	↑		C
Fusobacteria	↑		C
Bacteroidetes		↓	C
Antibiotics treatment			
Benefit effect of antibiotics treatment on survival	+		A

* Results were classified according to quality of evidence (see Methods). Reference sources were cited in **Suppl. Table S1** in Supplementary data.

Table 2: Mortality rates of Kwashiorkor and Marasmus in studies of malnourished children admitted to hospital

Sources	Marasmus*	Kwashiorkor*	Marasmic-Kwashiorkor*
McLaren, 1969	17.6%	39.9%	28.8%
Van den Broeck, 1993	8%	9%	
Schofeild and Ashworth, 1996	24%	30.1%	32.3%
Bailey, 1963	11%	14%	11%
Munthali, 2015	51%	55%	42%
Wammanda and Adeleke, 2002	21.8%	28.6%	42.9%
Laditan and Tindimebwa, 1983	25%	30%	21.87%
Amsalu and Asnakew, 2006	14.5%	16.9%	28.4%
Trehan, 2016	6.9%	3.2%	14.7%

* Color coded for form of SAM which had the highest mortality rate.

Table 3: Potential specific characteristics for Kwashiorkor or Marasmus

Characteristics	Kwashiorkor	Marasmus	Confirmed by meta-analysis*
Clinical features			
Oedema	+++		
Depigmentation skin, flag sins, flaky paint, crazy paving	+		
Loss of subcutaneous fat		+	
Dry skin, wrinkled, and loose		+	
Liver			
Enlarged liver	+		
Fatty liver	+		A
Aflatoxin detected in liver	+		
Biological markers (activity in serum or plasma)			
Glutathione	↓		A
Methionine (Sulfur-containing amino acid)	↓		A
Free circulating iron	↑		C
Na+/K+ pump sites	↑		B
Gut microbiota			
Pathogenic species proliferation	+		
Proteobacteria	↑		
Fusobacteria	↑		
Bacteroidetes		↓	
Antibiotics treatment			
Benefit effect of antibiotics treatment on survival	+		A

* Results were classified in category A, B, C, D. Reference sources were cited in Supplementary data