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The U.S. Government's Global Hunger & Food Security Initiative

EatSafe: Evidence and Action Towards Safe, Nutritious Food

Literature Review Linking Food Safety and Nutrition

Revised - November 2020

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This EatSafe report presents evidence that will help engage and empower consumers and market actors to better obtain safe nutritious food. It will be used to design and test consumer-centered food safety interventions in informal markets through the EatSafe program.

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ACRONYMS

CI	Confidence interval
CGIAR	Consultative Group on International Agricultural Research
CIAT	International Center for Tropical Agriculture
CIMMYT	International Maize and Wheat Improvement Center
CrI	Credible interval
DALY	Disability adjusted life year
EAEC	Enteroaggregative Escherichia coli
EHEC	Enterohemorrhagic Escherichia coli
EPEC	Enteropathogenic Escherichia coli
IFPRI	International Food Policy Research Institute
IGF-1	Insuline-like growth factor 1
ILRI	International Livestock Research Institute
LAZ	Length/height-for-age z-score
LMIC	Low- and middle-income country
PCB	Polychlorinated biphenyls
POPs	Persistent organic pollutants
p,p'-DDT	p,p'-Dichlorodiphenyltrichloroethane
p,p'-DDE	p,p’-Dichlorodiphenyldichloroethylene
SDG	Sustainable Development Goals
TNF-αRI	Tumor necrose factor αRI
UI	Uncertainty interval
WAZ	Weight-for-age z-score
WHO	World Health Organization
WHZ	Weight-for-height z-score

EXECUTIVE SUMMARY

Food safety is a major and persistent threat to the nutritional status of populations globally and is increasingly jeopardizing the effectiveness of public health programs. The burden of foodborne disease (FBD), estimated to be of the same order of magnitude as the burden of the "big three" (malaria, HIV/AIDS, and tuberculosis), is expected to be further exacerbated by the ongoing pandemic and its impact on food systems globally. Our progress toward the 2nd United Nations Sustainable Development Goal (SDG) to "end hunger, achieve food security and improved nutrition and promote sustainable agriculture" by 2030 may not be realized if we do not ensure food safety across the value chains to provide safe and nutrient-rich food to a growing global population.

Unsafe food can cause a variety of acute and chronic health impacts ranging from mild to debilitating or even life-threatening. In addition to increased morbidity and mortality, unsafe food results in significant socioeconomic impacts through healthcare costs and lost productivity, as well as harm to trade. There is evidence that foodborne disease also impacts outcomes that are also associated with nutrition, such as stunting and wasting. However, data on this component of the FBD burden and its underlying mechanisms are far from complete. Individuals in low-resource settings are considered to be particularly vulnerable to the effects of foodborne disease and associated nutrition impacts. However, more complete and accurate epidemiological data are needed to truly assess the impacts of foodborne diseases and their association with health and nutrition outcomes.

The aim of this report is to provide an overview of cross-pathways linking food safety/foodborne illness and nutrition and their shared impacts on health, while highlighting research gaps and opportunities for intervention. This body of evidence is meant to support the development of a framework linking food safety and nutrition, as part of Feed the Future and EatSafe programming.

The review specifically focuses on the health implications of food safety on nutrition-relevant outcomes. In this context, food safety includes acute and long-term physiological impacts. Health-related nutrition outcomes considered include gut health, nutrient absorption,

growth, and development outcomes, as well as outcomes related to metabolic and perinatal development.

The literature search was carried out in PubMed using an a priori developed search strategy, complemented by additional resources (CGIAR, CYMMIT, ICRISAT, FAO, IFPRI, WHO, World Bank). Where available, we leveraged information from existing reviews in lieu of original research articles. The review covers the connections between foodborne hazards and nutrition-relevant outcomes, including in the context of vulnerable populations. The Discussion contextualizes findings and highlights research gaps and limitations.

We identified clear linkages between some foodborne hazards and nutrition-related outcomes. However, the reviewed evidence does not allow for a clear attribution of causality. For instance, a strong relationship between gastrointestinal illness and growth impairment in children has been documented, but the extent of this impact and the underlying mechanisms are incompletely understood. Our findings also indicate a negative impact of certain hazards on nutrient absorption, growth outcomes, and metabolic functions. However, many of the reviewed studies have methodological limitations that can impede the ability to compare and contextualize findings within and between study populations. Nevertheless, we found some evidence for increased vulnerability to adverse nutrition outcomes from foodborne disease in specific populations including children, food handlers, women, pregnant women, and the elderly. Overall, additional research is warranted to effectively understand underlying mechanisms and potential group-specific interventions in more detail.

We found little evidence for the impact of pharmacological treatments of foodborne disease on nutritional outcomes, which may in part be due to limitations in our search strategy. Associations of antimicrobial treatment with diarrhea have been reported, while other evidence indicate a growth-promoting effect. Nausea can be a side effect of antiamebic and anthelmintic treatments; however, it is unclear whether and to what extent this affects nutrient intake and long-term nutrition outcomes.

In conclusion health-based connections between food safety and nutrition exist but are complex and often difficult to disentangle. Addressing existing data gaps on foodborne disease prevalence in many regions of the world is a key gap. An important related step would

be to harmonize measures and metrics for research protocols used for investigating this topic. In addition, longitudinal studies with frequent follow-ups could allow for a more granular assessment and potential attribution of health outcomes to a specific food hazard.

1. INTRODUCTION

Current estimates from the Global Nutrition Report indicate that one in three people worldwide are affected by malnutrition, which can broadly include features indicative of undernutrition, poor micronutrient status, or overweight and obesity. Increasingly, evidence is also suggesting a double burden of malnutrition in many of these individuals where undernutrition coexists with overweight, obesity and other diet-related non-communicable diseases (1). This double burden of malnutrition creates unique societal challenges with potential negative impacts on health-care costs, productivity, and economic growth, particularly in low-resource populations (2).

Nutritional insults (e.g. inadequate micro- or macro-nutrient supply) during certain life stages may have both short-term and long-term consequences, including intergenerational effects. Tackling malnutrition in all its forms requires that nutritional needs are addressed through the entire life-course (2). With diet-related factors consistently ranked as the top modifiable risk factor for morbidity and mortality worldwide, it is critical to understand and intervene on any challenge to diet and nutrition, including food safety. During the current COVID-19 pandemic, an even greater number of people may be affected by further food shortages, foodborne threats, and nutrition challenges.

Unsafe food creates a vicious cycle of disease and malnutrition, which particularly affects infants, young children, elderly, and the sick (3). Ensuring food safety is critical for optimal nutrition and health, and effective food safety management at the national level involves multiple stakeholders operating under diverse environmental, infrastructural, and socio-political conditions (4). Threats to food safety can occur at any stage of the value chain from production to consumption and can range from contamination with pathogens or toxins to use of unsafe additives as well as unsafe handling or storage that exacerbates risk.

The World Health Organization (WHO) defines foodborne disease as "*a disease commonly transmitted through ingested food. FBDs [Foodborne diseases] comprise a broad group of illnesses, and may be caused by microbial pathogens, parasites, chemical contaminants and biotoxins*" (5). In 2010, 31 foodborne hazards (including 11 diarrheal disease agents, 7 invasive infectious disease agents, 10 helminths, 3 chemicals) combined were responsible for 600 (95% uncertainty interval, UI: 420 – 960) million episodes of foodborne illnesses and 420 000 (UI: 310 000 – 600 000) deaths in addition to 33 million disability adjusted life years (DALYs). Data for 5 additional hazards of importance (4 bacterial, 1 chemical), were only available for subregions and did not allow for global estimates (5).

Symptoms associated with foodborne disease are manifold and range from mild and self-limiting (e.g. nausea, vomiting, diarrhea) to debilitating and life-threatening (e.g. kidney and liver failure, brain and neural disorders, paralysis, and potentially cancers), and can lead to long periods of absenteeism and premature death (5). The highest foodborne disease burden is seen in LMICs in Africa, South-East Asia, and the Eastern Mediterranean, this considerable gap between low- and high-income regions suggests that a major proportion of the foodborne disease burden is avoidable (5).

Access to safe food is key to allow individuals to benefit from its nutritional benefits. While it is generally accepted that compromised food safety is detrimental to the health of individuals or even populations, the linkages between a lack of food safety and nutrition outcomes are poorly understood and not quantified. The "chicken and egg" lack of data and adequate metrics and measures also hinders progress towards a quantification of this burden. This is particularly concerning given the broad impact on the food supply chain and often chronic health consequences of unsafe food in addition to its socioeconomic impacts.

In this review, we aim to synthesize the available knowledge and provide an overview of main physiological pathway linking foodborne illness to nutrition outcomes, also in the context of vulnerable populations. In the Discussion section we contextualize and discuss findings, highlight evidence gaps, and provide suggestions for future research directions. A pictorial schematic of key health outcomes considered in the review is shown in **Figure 1**.

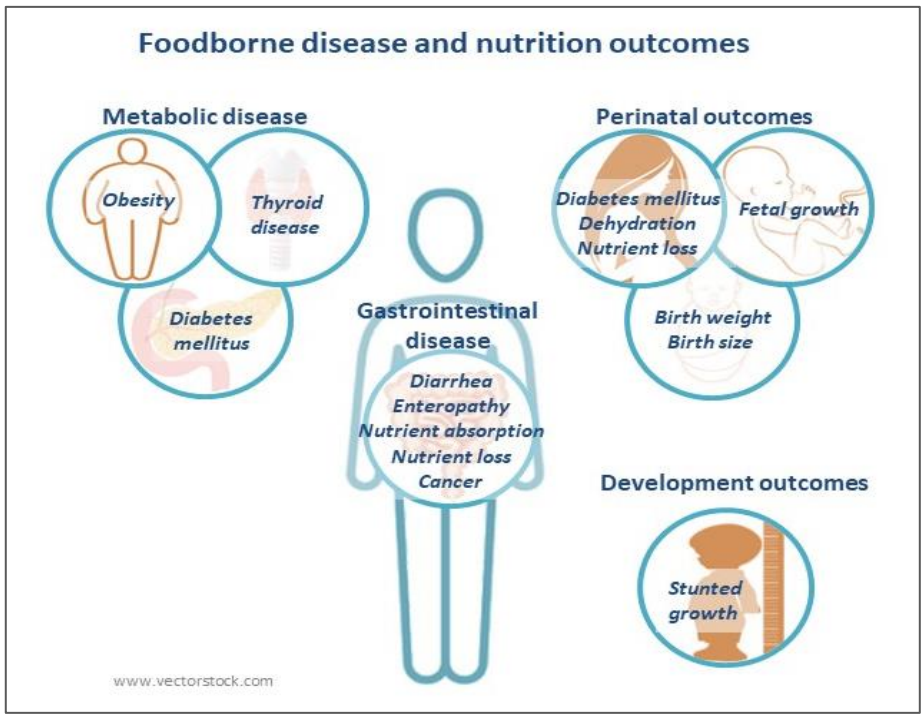

Figure 1. Illustration of key nutrition-relevant outcomes considered in the review.

2. METHODS

2.1. Outcomes of interest

Outcomes of interest, for the purposes of this review, are mainly physiological impacts of food safety on nutrition outcomes (**Table 1**).

Table 1. Food safety and nutrition outcomes considered in this review.

Food safety and foodborne disease	
Health outcomes	Physiological manifestation of foodborne disease (e.g. gastrointestinal illness), acute and long-term
Nutrition-related outcomes	
Food consumption	Adequate intake of nutritious food and ability to properly digest it
Nutrient absorption	Micronutrient absorption and deficiency, ability to assimilate food
Development	Stunting, wasting, malnutrition-related metrics

Perinatal/reproductive health	Newborn growth, placental/fetal development, gestational diabetes, preeclampsia and its impacts
Other outcomes	E.g. gastric cancer, metabolic diseases such as type 2 diabetes mellitus, overweight/obesity, thyroid disease

2.2. Literature search protocol

This review aims to identify and describe linkages between food safety and nutrition-related outcomes. A key objective is to synthesize the available evidence on food safety in the context of nutrition outcomes, to identify evidence gaps, and make recommendations for policy makers and researchers to fill those gaps.

We reviewed the food safety literature and identified studies through a search strategy that was developed a priori in collaboration with an experienced librarian. The search was completed in PubMed and retrieved an initial set of 8336 non-duplicate items. Titles and abstracts in this initial set were screened by one reviewer. Of all identified titles and abstracts, 276 full texts were screened. Reasons for exclusion included absence of links to nutrition outcomes, reports describing laboratory experiments or single outbreaks, and studies and reviews focusing exclusively on behavioral or economic factors. Systematic reviews were considered whether or not they focused on outcomes in LMICs. This search strategy was complemented by a review of articles from selected relevant resources (CIAT, CGIAR, CIMMYT, IFPRI, ILRI, WHO, World Bank, World fish). Furthermore, we screened reference lists of relevant articles to identify relevant literature that was not captured by the search strategy. Where available, we included evidence synthesized in identified (systematic) literature reviews in lieu of primary research articles. A total of 86 studies were included in the review.

3. RESULTS

Our search revealed 52 articles from the linkages between foodborne disease and physiological outcomes that we considered relevant for inclusion in this review, including 26 systematic reviews, 16 reviews, 10 original research/other articles.

3.1 Physiological impacts of foodborne disease on nutritional outcomes

The largest body of evidence directly linking food safety to nutrition and health outcomes pertains to foodborne illness, though most of it is from high-income settings. We considered a total of 51 articles in this section. Of those, 26 were systematic reviews (with or without meta-analyses), nine reviews (non-systematic), as well as seven articles other articles (primary research, burden of disease, risk assessment, or policy documents). Different hazards may elicit physiological mechanisms and consequently affect nutrition outcomes via different pathways, summarized in Tables 2, 3, and 4. Evidence is strong for a relationship between gastrointestinal illness and growth impairment; however, the extent of this relationship and underlying mechanisms are not well understood. The synthesized evidence also suggests a negative impact of certain hazards on nutrient absorption (e.g. helminths, *Helicobacter pylori*), growth outcomes (e.g. mycotoxins, arsenic), metabolic functions such as glucose and thyroid metabolism (e.g. persistent organic pollutants and other chemicals), as well as gastrointestinal ulcers (*Helicobacter pylori*). In addition to short-term consequences, foodborne diseases can have a variety of long-term health implications. These consequences are manifold and include impaired growth and development, cognitive decline, as well as negative impacts on reproductive and metabolic processes.

3.1.1. Impact of foodborne gastrointestinal illness

Diarrhea

Diarrhea is the most common manifestation of food borne disease caused by microbial hazards, and results from excessive secretion and/or impaired absorption of fluid and electrolytes across the intestinal epithelium. Undernourished or unwell children are at a higher risk of subsequent infection and mortality compared to healthy ones, which may result in a bi-directional positive feedback loop in which childhood undernutrition and diarrhea each increase the risk of the other (6). A systematic review conducted in 2018 on the etiology of gastroenteritis and acute diarrhea among children <5 years of age reports that viruses accounted for the majority (50.2%) of cases followed by bacteria (31.6%), and parasites (12.1%). Rotavirus was the most common etiologic agent of acute diarrhea (29.2%) in all

regions followed by *Escherichia coli* (15.6%) and Adenovirus (10.8%), with *Giardia lamblia* (7.3%) being the most prevalent parasite (7).

Environmental enteropathy (environmental enteric dysfunction)

Environmental enteropathy describes a reversible subclinical state of intestinal inflammation in response to enteric pathogens. It is characterized by gut mucosal cell villous atrophy, crypt hyperplasia, increased permeability, and inflammatory cell filtrate. The mechanisms underlying environmental enteropathy are incompletely understood. Evidence suggests that the hyper-stimulated gut immune system results in an inflammatory, hyper-immune state consequently causing a disrupted gut immune response, reduced delivery, absorption, and utilization of nutrients, thus causing nutritional deficiency (8). Furthermore, exposure to bacteria through fecal-oral transmission has been suggested to induce morphological changes in the intestine, thus leading to increased intestinal epithelial damage, permeability, and microbial translocation into the lamina propria. This causes an influx of inflammatory cells to the intestine, eventually leading to local and systematic inflammation (9).

Gastrointestinal illness and growth impairment

Short-term associations between diarrhea and weight loss are well-accepted; however, long-term associations between diarrhea and growth are less well defined (10). A framework of primary drivers of stunting in low-resource settings informed by population attributable factors suggests that among five identified child-level risk factor categories (infection, diet, birthweight, pollutants, environmental enteric dysfunction), infections (i.e. diarrhea, HIV, malaria, respiratory illness, helminths) contributed most to stunting. Furthermore, diarrhea was the greatest single cause of stunting, indicating that the burden of mild diarrheal disease remains a key contributor to sub-optimal child growth with a potential long-term effect on child development and adult health (11).

The systematic review investigating diarrheal disease mortality in children <5 years of age reported that each day with diarrhea was associated with decreased height-for-age (LAZ), weight-for-age (WAZ), and weight-for-height (WHZ) z-scores (6). Pathogens causing food-borne outbreaks such as *Clostridium perfringens* or *Staphylococcus aureus* producing

enterotoxins were excluded from the review due to the scarcity of available data with respect to their importance in developing countries (12).

A secondary data analysis of 7 cohort studies from 4 countries (Bangladesh, Brazil, Guinea-Bissau, Peru) conducted between 1985 and 1997 showed an association between diarrhea and a small but measurable long-term decrease in linear growth. The study showed that 10 additional days of diarrhea/child/year of follow-up had a negative relationship with LAZ at 24 months of age (change in LAZ: −0.1, 95% CI -0.1, -0.0; P= 0.000). The cumulative association between the average diarrhea burden (equivalent to 23 diarrhea days/year) and length at age 24 months was −0.38 cm (95% CI: -0.59, -0.17). This indicates that days with diarrhea during individual months had little apparent relationship with linear growth. However, cumulative diarrhea episodes demonstrated a small but measurable association between diarrhea burden and linear growth. Thus, any single episode of diarrhea during childhood seemingly only has a small relationship with linear growth and can be recovered through catch-up growth, provided adequate illness-free time. However, when accumulated throughout the first 24 months of life, diarrhea may be associated with a loss in height potential (10). This 'double burden' of diarrhea and malnutrition may make children with stunted growth and repeated gut infections at increased risk of developing obesity and its associated comorbidities, thus representing a 'triple burden' of the impoverished gut The mechanism is not completely understood, but nutrient deprivation as well as other potential insults (e.g. maternal stress, inflammation) during gestation have been suggested to cause epigenetic changes such as DNA methylation and histone acetylation, modifying expression of genes related to metabolism and growth, particularly insulin growth factor-2 (IGF-2) to prepare the individual for potential future caloric deficiencies (reviewed in (13) with reference to 3 longitudinal and 2 cross-sectional studies).

The global burden of diarrheal disease among children below 5 years of age in 188 countries was reviewed in the context of different diarrhea-associated sequelae. The findings suggest that an episode of diarrhea can lead to a potential pathogen-specific diversity loss in gut microbial communities. Poor composition of the microbiota may contribute to malnourishment, reduced response to oral vaccines, increased susceptibility to additional infections, and the promotion of inflammation (9).

Another review suggests a strong association between stunting and early-childhood diarrhea in general, and with *Cryptosporidium*, *Entamoeba histolytica*, and *Shigella* infection in particular. Apart from macronutrient malabsorption resulting from environmental enteropathy or other pathways, children may experience appetite suppression and may be fed lower than usual amounts. In addition, systemic or intestinal inflammation due to bacterial translocation can negatively regulate insulin-like growth factor 1 (IGF-1; lower levels of IGF-1 have been suggested to mediate stunting in early life due to IGF-1's function at growth plates (14)), thus inhibiting growth (15).

Environmental enteropathy, rather than diarrhea, has been proposed as primary causal mechanism between poor water, sanitation, and hygiene practices and stunting. Pathways by which enteropathogenic infections may lead to chronic health consequences are complex and not fully understood. Intestinal inflammation as a result of infection with enteropathogenesis and distortion of the intestinal barrier and absorptive function have been suggested to imply changes in the host microbiome. While malabsorption itself can contribute to growth faltering, changes in the microbiome may lead to autoimmune dysfunction (15).

As described above intestinal morphological and subsequent intestinal epithelial damage, permeability, and microbial translocation resulting from environmental enteropathy cause an influx of inflammatory cells eventually leading to local and systematic inflammation. Resources that would be normally directed toward child growth and development are reallocated and hormonal pathways that regulate growth plate activity in long bones are disrupted. Chronic inflammation and reduced intestinal nutrient absorption are also hypothesized to affect brain development, inducing lasting negative effects on cognition, educational achievement, and linear growth (9). The above-described nutritional deficiency impairs the renewal of epithelial tissue as well as the maturation and proliferation of intestinal and pancreatic ß-cells resulting in linear growth faltering. In addition, the low-grade inflammatory state concurrently impedes bone growth, and consequently height, by inhibiting endochondral ossification (8).

A systematic review from 2018 assessed the relationships among five environmental enteric dysfunction domains (i.e. intestinal damage and repair, permeability and absorption, microbial translocation, intestinal inflammation, systemic inflammation) and between each

domain and stunting. The review questions a direct relationship between intestinal permeability (i.e. small pores between epithelial cells allowing for paracellular permeation of e.g. lactulose) and microbial translocation (i.e. passage of microbes/microbial products through the epithelial barrier into the lamina propria and local mesenteric lymph nodes) and between microbial translocation and stunting. Rather, the authors suggest inconsistent and variable relationships between environmental enteric dysfunction domains, while strong evidence supports the relationship between intestinal inflammation and systemic inflammation as well as between intestinal inflammation and stunting (9). A recent study in Tanzanian children further reported a significant association between systemic inflammation at six weeks of age and stunting (HR 2.14, 95% CI: 1.23, 3.72; p = 0.002) (16).

Factors other than microbial translocation, such as pathogen colonization with subsequent changes in the intestinal microbiota, may be responsible for intestinal inflammation in individuals with environmental enteric dysfunction. The authors speculate that environmental enteric dysfunction is not a single entity, but rather a set of phenotypes dependent on unique environmental exposures with geographic variations. Small intestinal bacterial overgrowth may also contribute to intestinal inflammation and environmental enteric dysfunction; however, evidence for a relationship between stunting and small intestinal bacterial overgrowth is lacking (9).

Mycotoxin exposure has been associated with environmental enteropathy. Three biologically plausible pathways through which aflatoxin exposure may affect growth have been suggested. These include 1) zinc deficiency, 2) inhibition of protein synthesis resulting in impaired metabolism, as well as 3) enterocyte damage ultimately leading to systemic immune activation. Similarly, suggested causal pathways for fumonisin exposure include decreased food intake and an inhibited sphingolipid metabolism, which may cause a degradation of epithelial barrier and stimulation of an inflammatory immune response. Human evidence for pathological effects of other mycotoxins such as deoxynivalenol and zearalenone is scarce, however, rodent studies indicate a negative effect of deoxynivalenol on growth due to reduced food intake and weight gain (17).

3.1.2. Impact of foodborne disease on nutrient absorption

The morbidity impact of enteric pathogens is to a large extent due to their ability to directly impair intestinal nutrient absorption (18). Efficient digestion of food constituents depends on various, interconnected processes (e.g. secretion of intraluminal enzymes and bile salts; regulation of intraluminal pH, transit of intestinal contents), pathogens may alter each of these processes by causing hypochlorhydria, by physically blocking pancreatic or biliary ducts, by damaging the mucosal surfaces, or by hastening peristaltic propulsion (19). Several foodborne pathogens may impact the absorption of different nutrients; however, evidence seems strongest for the effect of helminths and *Helicobacter pylori*.

The detrimental impact of helminth infections on nutrient status has been attributed to intestinal inflammation and obstruction, appetite loss, as well as blood loss due to internal bleeding. Negative associations between helminth infection and serum retinol (used to determine vitamin A deficiency in populations (20), but not serum ferritin (used to determine iron status in individuals and populations (21) were identified, however, deworming led to a rise in hemoglobin (used for the diagnosis and classification of anemia (22)) (23-26).

An impact of *Helicobacter pylori* on nutrient status has been suggested through changes in gastric physiology and histology, as well as impaired nutrient uptake. Evidence from systematic literature reviews indicates *Helicobacter pylori* associated increases in iron deficiency, anemia, and iron deficiency anemia. Furthermore, an association with lower cobalamin and folate levels as well as lower levels of ascorbic acid in plasma and gastric juice have been reported. In addition, *Helicobacter pylori* eradication had a positive effect on ascorbic acid in gastric juice and serum cobalamin (27-30).

3.1.3. Impact of foodborne disease on perinatal/reproductive health

Foodborne disease may impact perinatal health outcomes (e.g. gestational diabetes, fetal development, via different mechanisms (e.g. changes in glucose metabolism, dehydration; **Table 1**. In addition to impacts on the health and nutritional status of the pregnant woman, foodborne hazards can affect the development and health of the fetus, and hence the newborn.

Helicobacter pylori affects perinatal outcomes through suggested effects on glucose metabolism and endothelial damage. Meta-analyses showed significant associations between *Helicobacter pylori* infection and antenatal hyperemesis gravidarum (38 studies), fetal growth restriction (16 studies), gestational diabetes (reports from 3697 cases), as well as low birth weight (8 studies) (31, 32).

Meta-analyses showed associations between *Vibrio cholerae* and fetal (4 studies), neonatal, and maternal death (9 studies each). Suggested mechanisms include maternal and fetal acidosis as well as electrolyte changes in the amniotic fluid resulting from severe vomiting (33, 34). *Toxoplasma gondii* and *Listeria monocytogenes* are two key bacterial pathogens associated with adverse reproductive outcomes. *Toxoplasma*, which can be transmitted vertically from expectant mother to fetus, may result in severe negative outcomes on fetal development, ranging from fetal growth restriction (FGR), preterm birth, fetal anomalies, and congenital toxoplasmosis (frequently resulting into ocular lesions, mental and growth retardation, and other issues related to nerve development) to fetal death (35, 36). Listeria monocytogenes also has a higher prevalence, higher severity during pregnancy, in addition to a high rate of fetal deaths, preterm births, and fetal distress (37). While direct mortality outcomes are outside the scope of this review (i.e. for this review death from a foodborne illness is considered a direct outcome of the illness, not mediated by nutrition factors, and hence excluded from the discussion on links between food safety and nutrition), they should be kept in mind as the extreme boundary of both foodborne hazard and nutrition impacts.

A systematic review published in 2020 suggests an association between mycotoxin exposure and intrauterine fetal growth restriction, whereas evidence regarding perinatal death, preterm birth and decreased birthweight is inconclusive (38).

Arsenic exposure is also thought to affect perinatal outcomes, namely low birth weight, preterm delivery, birth weight decline, as well as decreased birth size. The available evidence is minimal and mostly relies on cross-sectional studies. Inorganic arsenic can accumulate in the placenta where it may disrupt and alter cord blood methylation, in addition, arsenic can also cross the placenta and accumulate in developing fetal organs However, no meta-analysis was conducted as reviewed studies examined different mycotoxins and outcomes with different effect measures (39-41).

3.1.4. Foodborne diseases with impact on metabolic processes

Glucose metabolism

Foodborne disease can impact glucose metabolism through altering the host's receptors and/or autoimmune response. A review of 7 case-control studies suggests chronic toxoplasmosis as possible risk factor for type 2 diabetes mellitus, while there is no significant association with type 1 diabetes mellitus. Suggested mechanisms include auto-immune and inflammatory processes in addition to a direct invasion, destruction of pancreatic b-cells, intracellular pathogen stimulation, as well as impaired phagocytosis and increased susceptibility to opportunistic infections (42). Phthalates may promote type 2 diabetes through receptor alteration and induction of oxidative stress; however, evidence is limited. The single prospective study that examined incident diabetes as an outcome reported strong associations for multiple phthalates, and several studies reported associations with insulin resistance (43).

Thyroid function

Most animal studies show anti-thyroid effects upon high nitrate/nitrite exposure; however, this has so far not been confirmed in humans. Nitrites and nitrates can inhibit iodine uptake which may subsequently lead to decreased thyroid hormone production. Chronic thyroid gland stimulation may induce a change of follicular cells and hypertrophy or hyperplasia.

A meta-analysis showed no significant association between nitrate exposure and the risk of thyroid cancer, hyper- and hypothyroidism. However, three cohort studies showed a significant association between higher exposure to nitrite and the risk of thyroid cancer (risk = 1.48, 95% CI = 1.09–2.02, P = 0.012) (44).

Obesity

Exposure to persistent organic pollutants (POPs), polychlorinated biphenyls, and bisphenol A has been associated with obesity due to impaired thermogenesis and increased adipocyte cell differentiation, respectively. Evidence for an obesogenic potential of POPs is mainly derived

from in vivo studies, for polychlorinated biphenyl (PCB) and bisphenol A evidence is available from observational studies (45, 46).

Cancer outcomes

Foodborne pathogens are associated with different forms of ulcerative disease or cancer at various body sites (e.g. skin, lung, liver). This review focuses on ulcers/cancers directly impacting the gastrointestinal tract. Meta-analyses of 46 studies from 24 countries indicated a 1.26-fold risk for peptic ulcer for *Helicobacter pylori* infection. Furthermore, *Helicobacter pylori* eradication was significantly associated with decreased risk of gastric cancer. It has been suggested that chronic gastric inflammation may lead to precancerous changes of atrophic gastritis and intestinal metaplasia, whereas chronic infection may cause hypochlorhydria (47-49).

3.1.5. Impacts of foodborne disease treatment on nutritional outcomes

In this section we briefly highlight examples of treatments of foodborne disease in respect to their potential impact on nutrition outcomes. As this assessment was not the primary objective of our review it is not meant to be exhaustive, but rather aims to complement other sections of this review. Seemingly, the evidence linking a specific treatment to adverse nutrition outcomes is scarce. A more targeted systematic review may allow for elucidating this issue further and can provide a broader context to inform future research efforts. Evidence for this section was compiled from three systematic reviews, two reviews (non-systematic), and one cohort study.

Treatment of infectious enteric disease with antimicrobials

Antibiotic treatment of infectious enteric disease may yield profound effects on the composition and function of the gastrointestinal microbiome. Specific classes of agents (e.g. β-lactams, fluoroquinolones) predispose subsets of individuals to antibiotic-associated diarrhea and colitis due to specific pathogens. Antimicrobial-associated disorders result from the short- and long-term impacts of antibiotics on the composition and function of the human microbiome. Perturbations of the gastrointestinal microbiota create opportunities for bacterial proliferation and disease. Disease may result from toxin production, which may

result in symptomatic diarrheal illness. The primary etiologic agent of antimicrobial-associated diarrhea, toxigenic *Clostridium difficile*, accounts for an estimated 15%–25% of cases. Other agents that have been associated with antimicrobial associated diarrhea include clostridial etiologies (including enterotoxin-producing strains of *Clostridium perfringens* and possibly *Clostridium spiroforme*) as well as enterotoxin-producing strains of *Staphylococcus aureus* (50). Interestingly, a meta-analysis of ten randomized controlled trials indicates that antibiotic use increased height and weight, with larger effects on height in younger populations. This antibiotic growth promoting effect may be mediated by treatment of clinical or subclinical infections or by modulation of intestinal microbiota (51, 52).

Deworming

Deworming via preventive chemotherapy is carried out to lower the burden of helminth infections and improve development outcomes (e.g. height and weight gain) (53). A Cochrane systematic review of 52 studies carried out in 2017 and assessing the effects of mass deworming on health outcomes found little evidence of adverse events from deworming, including impacts on nutrition outcomes (54). The review found that mass deworming for soil-transmitted helminths with albendazole twice/year compared to controls had little to no improvement in weight or height over a period of about 12 months (0·09 kg, 95% credible intervals [CrI] -0·04, 0·20 and 0·07 cm, 95% CrI -0·10, 0·24, respectively; moderate certainty evidence), little to no difference in weight-for-height (0·14, 95% CrI -0·20, 0·47; high certainty evidence), proportion stunted (eight fewer per 1000 children, 95% CrI -48, 32; high certainty evidence), or mortality (one fewer per 1000 children, 95% CI -3, 1; high certainty evidence). Administration of albendazole led to minimal adverse events (moderate certainty evidence) and no studies reported cases of intestinal obstruction. Of the included studies, 2 studies reported that effects of deworming were not sustained once deworming was ceased (moderate certainty evidence) (54).

Antiamebic treatment

Another Cochrane systematic review from 2019 investigated the effects of antiamebic drugs for treating colitis. Of the 41 included trials, 37 reported predominantly gastrointestinal adverse events, such as nausea, vomiting, anorexia, bitter or metallic taste, and abdominal

discomfort. The authors conclude that, compared with metronidazole, tinidazole may be associated with fewer adverse events (moderate-certainty evidence) while also being more effective in reducing clinical failure (low-certainty evidence) (55). Similar findings were reported by a systematic review conducted in 2007 that assessed adverse effects of drug treatments for amebic dysentery in endemic areas. The study found that ornidazole may be more effective at curing amebic dysentery compared to placebo but that this treatment may cause nausea and vomiting. Furthermore, it was unclear whether tinidazole performed better than placebo, but tinidazole outperformed metronidazole with fewer adverse effects (very low-quality evidence) (56). Such side effects may detrimentally affect nutrient status due to reduced food consumption as well as impaired nutrient absorption and possible disruptions of physiological gastrointestinal mechanisms.

3.1.6. Foodborne disease and nutrition outcomes in vulnerable populations

Foodborne pathogens may take advantage of weakened immune systems, putting vulnerable populations such as infants and young children, pregnant women, the elderly, and immuno-compromised individuals at particular risk of contracting common food-related diseases (5). In addition, infants and pregnant women often have different consumption patterns and nutrient requirements compared to other family members, potentially affecting their exposure to certain food-associated hazards (57). In this section, we compiled evidence from ten reviews (two systematic, eight non-systematic) and one orginal research article. While it seems intuitive that foodborne disease affects nutrition outcomes in vulnerable populations, surprisingly little evidence in this area is available. Specifically, it is unknown whether and to what extent vulnerable populations (compared to non-vulnerable ones) are more susceptible to short- and long-term adverse etiologies of nutritional outcomes linked to fodborne diseases.

Populations affected by malnutrition

Low weight, particularly weight-for-height, is a serious risk factor for infectious diseases, with possible immediate, acute negative effects on systematic and mucosal immune system functions (13). A systematic review on immune function in children with malnutrition that was conducted in 2014 found associations of malnutrition with impaired gut-barrier function,

reduced exocrine secretion of protective substances, and low levels of plasma complement. The authors suggest that immunological alterations associated with malnutrition in children may contribute to increased mortality; however, the underlying mechanisms are not completely understood (58).

Several studies suggest that malnourished individuals are particularly susceptible to detrimental arsenic-related health effects (with arsenic exposure being primarily via food ingestion). In utero and/or early-life arsenic exposure has been linked to increased mortality due to multiple cancers, lung disease, heart attacks, and kidney failure as well as detrimental effects on cognitive development, intelligence, and memory later in life (41).

Undernutrition is both a sequela of, and a risk factor for, cryptosporidiosis, particularly in children (59). A triple-cohort study in Haitian children <18 months of age (children with cryptosporidium and diarrhea, diarrhea only controls, healthy controls) demonstrated that children with acute cryptosporidiosis were more malnourished compared to both control groups and also had elevated markers of proinflammatory immune response [e.g. tumor necrose factor αRI (TNF-αRI) was elevated in 21 of 28 case patients (P=.004) to a maximum of 4809.7 pg/mL; furthermore, among cases with detectable fecal lactoferrin, all TNF-αRI levels were >200 pg/mL (range, 220–3559 pg/mL)] (60). The Cryptosporidium burden was highest in children <1 year amounting to nearly 250 DALYs per 1000 child-years in sub-Saharan Africa in this age group with most of this burden attributable to long-term outcomes associated with undernutrition (59).

Children

Children <5 years of age carry a large proportion (40%) of the disease burden attributable to foodborne hazards, despite representing only 9% of the global population (5). Malnourished infants and children are at higher risk of developing serious forms of foodborne diarrheal diseases, which can exacerbate malnutrition, thus leading to a vicious circle of debilitation and mortality and preventing many from reaching their full potential in society (5). Children are also more vulnerable to the consequences of infection because of their developing immune system, small body size, lower levels of gastric acid and other factors (57). In addition, children have an increased exposure to foodborne hazards because of their lack of control

over food preparation and may exhibit behaviors that can increase risk (e.g. eating soil or animal feces) (61).

Gender

Gender can be an important determinant of exposure of risk, often as a proxy of other underlying drivers. For instance, gender is often correlated with poverty and poverty in turn is associated with increased burden of both foodborne disease and malnutrition (62). Gender roles and occupations can also drive health outcomes. A recent assessment of 20 informal livestock and fish value chains found socially constructed gender differences as major driver of differences in health risks. With the exception of one study on listeriosis risk, differences in risk of foodborne disease were attributable to gender roles and occupation rather than biological sex. While men were most likely to suffer from occupational exposure and injuries associated with livestock production, fishing, hunting, and slaughterhouse work, women were more exposed to food-borne pathogens during processing, selling, and preparation of food (63). Another study argues that males may be at higher risk of exposure to occupational health hazards in the meat supply chain, because slaughtering is mainly performed by men (64). Studies on slaughterhouse workers have indeed highlighted deficiencies in food safety practices (64). Additional example of increased exposure to foodborne or zoonotic pathogens include vendors and workers in informal markets, who are in more frequent and close contact with food and food-contact surfaces (65). Increased impacts on nutrition outcomes could be inferred – albeit not yet well supported by data – as a consequence of increased foodborne or occupational exposure. In addition, preferential access to some foods by food producers may impact the composition of their diet.

Only one study on listeriosis risk identified differences in foodborne disease outcomes as attributable to sex or biology, as susceptibility to infection by *Listeria monocytogenes* is heightened during pregnancy (63). As another example, albeit without a hazard-specific link to nutrition outcomes besides gastrointestinal illness, in the adult population invasive amebiasis is more common in males than females, particularly for amebic liver abscess, while no gender difference is seen in children (66). These findings suggest that gender differences for some nutrition outcomes associated with foodborne disease may be more strongly

associated with gender roles and occupation, rather than biological sex differences. However, further investigation is warranted.

In contrast, a higher risk for developing post-infectious irritable bowel syndrome was associated with female gender, younger age, anxiety, long duration of diarrhea, and weight loss (67). Likewise, cohort studies in Bangladesh demonstrated possible sex-dependent associations between arsenic exposure and child growth in girls (39). Furthermore, a systematic review from 2011 found a gender effect for the association between exposure to PCB and obesity, with girls being more susceptible, whereas prenatal PCB exposure was associated with reduced birth weight predominantly among male infants (68).

Other vulnerable populations

Pregnancy, old age, and immune status can also result in increased vulnerability to foodborne hazards, and associated nutrition outcomes. For example, limited evidence based on epidemiological data suggests that listeriosis is more prevalent in pregnancy than in non-pregnant populations, with 16–27% of all *Listeria monocytogenes* infections occurring in pregnant women, which result in a high rate of fetal distress and miscarriage (37, 69). Nutrition outcomes associated with *Listeria* infection are described in Table 3. Likewise, old age as well as medical interventions that severely compromise the immune system greatly increase the susceptibility to acquiring listeriosis (70). While non-invasive forms of listeriosis cause symptoms such as diarrhea, fever, headache, and myalgia, listeriosis during pregnancy can cause prenatal fever, meconium-stained amniotic fluid, fetal distress, or even death (37). The host's innate and adaptive immunity also play a major in the severity of prognosis for cryptosporidiosis and giardiasis. Immunocompetent individuals typically experience self-limiting diarrhea and transient gastroenteritis and recover without treatment, suggesting efficient immune responses, whereas immunocompromised individuals including HIV/AIDS patients often suffer from potentially fatal intractable diarrhea (59).

4. DISCUSSION

In this review we summarized evidence on the linkages between food safety and nutrition by discussing key physiological effects of unsafe food, with a focus on health-related impact pathway linking foodborne diseases to nutrition outcomes. The risks associated with unsafe food consumption are undoubtedly substantial yet are not systematically quantified. Estimates attribute about one third of global diarrhea cases to foodborne disease. However, reliable data are lacking for several countries and regions. This uncertainty, as well as limited data to attribute disease burden to specific foodborne hazards or food categories limits the ability for an adequate response (71).

Foodborne disease burden is increasing in LMICs owing to increases in the consumption of animal-source foods, rapid lengthening and increasing complexity of value chains, as well as slow/missing improvements in food safety governance, among other factors (72). These impacts may not be felt equally across society. While cross-impacts between food safety and nutrition may be non-linear, arguably an increase in foodborne disease burden would also result in an increase in associated negative nutrition outcomes. We identified strong linkages between some foodborne hazards and nutrition-related outcomes; however, several gaps and limitations in the reviewed literature (discussed below) impair our full understanding and our ability to establish causality.

4.1 Physiological and public health implications

We consider the available evidence with regards to a relationship between pediatric gastrointestinal illness and growth impairment as strong. However, the extent of this relationship and underlying mechanisms are not completely understood. Furthermore, the exact determinants of gastrointestinal illness that may cause impaired growth as well as the impact of timepoint and duration of illness are still debated. Also, no clear evidence of an association between adult gastrointestinal illness and malnutrition emerged from the literature reviewed. Evidence also points toward a negative impact of certain hazards on nutrient absorption (e.g. helminths, *Helicobacter pylori*), growth outcomes (e.g. mycotoxins, arsenic), metabolic functions such as glucose and thyroid metabolism (e.g. persistent organic pollutants and other chemicals), as well as gastrointestinal ulcers (*Helicobacter pylori*). For some hazards (e.g. *Helicobacter pylori*), mechanisms are better understood, at least partially

because they have been investigated for decades, while research for other hazards is still in its infancy.

Studies investigating the relationship between pathogens and diarrheal disease present inherent limitations. Certain organisms may remain in the feces for a long time after an infection-causing illness, possibly leading to misclassification as a non-diarrhea causing agent. Similarly, longitudinal studies may identify long-term secretors after illness from asymptomatic infections (6). The systematic review investigating specific pathogens that may be associated with persistent diarrhea in children in LMICs found no evident association between a particular pathogen and persistent diarrhea (73). The review showed that both children with persistent diarrhea and without diarrhea carried a wide range of enteric pathogens with varying rates between studies. The authors highlight methodological limitations in the reviewed studies including varying designs, small sample sizes, and the assessment of different (combinations of) pathogens. Furthermore, the use of different classification systems in some cases prevented a combined analysis of data across studies (73). Other studies have identified additional gaps pertaining to methodological issues. Common gaps found in the studies include (1) lack of controlling for confounders such as e.g. previous health history, (2) duration of illness, (3) nutrient intake/status, seasonality, (4) exposure dose and duration as well as (5) exposure to other potential hazards. Furthermore, cross-sectional study designs, lack of representativeness of study populations, as well as small sample sizes have been recognized (29, 44, 47).

The review revealed other methodological limitations that, if addressed, could improve the evidence base on foodborne diseases' impacts on nutrition outcomes. In terms of burden assessment, for example, many foodborne hazards lack well-established biomarkers and/or cheap, readily available tools for their identification, which hinders exposure assessment and attribution, which are in turn needed for effective interventions. Furthermore, evidence from well-designed human studies is often lacking along with consistent clinical definitions (e.g. environmental enteropathy) and improved education of healthcare professionals regarding foodborne disease symptoms (9, 74, 75). Study findings may also be biased towards certain domains that are easier to measure compared to others (9).

While different aspects of food safety research have well-developed metrics, in many cases available metrics are not widely applied or not suited for widespread use (72). There are also no established approaches for assessing the proportion of adverse nutrition outcomes, such as wasting or stunting, associated with foodborne infections. Another challenge is the lack of specificity for some symptoms which may not allow for an accurate diagnosis, in addition to individuals not seeking healthcare. Both may lead to under-reporting and subsequent under-estimation of health-impacts in response to certain hazards. Many countries also lack adequate public surveillance systems to track foodborne disease. The resulting dearth of epidemiological data hinders the quantification of the full extent and cost of foodborne disease. In turn this prevents policy-makers from setting priorities and allocating resources towards improving food safety and associated nutrition outcomes (5). This is even more true for assessing impacts of foodborne disease on nutrition, for which data and evidence are largely lacking and are not accounted for in surveillance systems.

Other health implications, while not covered in depth in this review, warrant further attention. Pharmacological treatment of infectious foodborne disease may lead to short-term nutrition impacts, but evidence suggests this impact is minor. However, antimicrobial treatments can alter the intestinal microbiome in the short- and long-term, with poorly understood impacts on gut health. Holistic investigation of medium- to long-term impacts of certain foodborne disease treatments on health and nutrition outcomes, as well as socioeconomic outcomes are warranted. Also, there is limited available evidence regarding vulnerable populations and population-specific exposure and foodborne disease outcomes, as well as their implication for nutrition outcomes. Particularly, the role of sex and gender as determinants are not well understood or quantified.

4.2 Limitations and suggestions for future research

We aimed to provide a broad picture of the impacts of foodborne hazards and disease on nutrition-relevant outcomes, with a focus on low-resource settings. Given the high complexity of this topic, it was not possible to capture all impacts within a parent search strategy. Rather, we aimed to provide an overview of relevant issues and highlight evidence gaps to inform future research efforts. For instance other relevant health implications, such as impacts of foodborne disease on cognitive development or debilitating syndromes that impair individual

abilities to work or care for a family, are relevant in the context of overall health and nutrition outcomes but were outside of the scope of this review. In addition, the review focused on the impacts of food safety on nutrition outcomes, not vice versa. Lastly, strength of evidence was discussed throughout the review, but could not be quantified.

In the process of reviewing the existing literature on food safety impacts on nutrition outcomes, we also identified several gaps that could be filled by future research efforts:

- Harmonized metrics and rigorous research methods should be developed and applied across the disciplines of nutrition and food safety.
- Longitudinal studies are needed to assess temporal relationships and long-term impacts of foodborne disease on nutrition outcomes. Such studies should address sex-/gender-related aspects that may confound research findings.
- Inexpensive, readily accessible, and decentralized tools should be developed for reporting on relevant metrics to facilitate foodborne illness attribution to specific hazards and routes of transmission.
- The study of physio-pathological mechanisms of foodborne disease – including long-term health impacts – and their links to specific hazards should be strengthened and made more quantitative.
- Nutrition outcomes should be better accounted into the burden of foodborne diseases. However, data and methods do not currently allow for a satisfactory inclusion of these variables.

While a comprehensive review of socioeconomic processes linking food safety and nutrition was outside the scope of this review, the literature search also highlighted the dearth of evidence on the dietary and socioeconomic impacts of food safety and foodborne disease, on their own and as they relate to nutrition outcomes.

5. CONCLUSIONS AND IMPLICATIONS FOR EATSAFE PROGRAM DESIGN

This review documents linkages between food safety and nutrition. While in some cases the main mechanisms involved are known, these complex networks of causal physiological pathways are often difficult to disentangle. In general, there is more evidence regarding the impact of foodborne diseases on health and nutrition-relevant outcomes, than on the opposite direction of impact, i.e. impacts of malnutrition on vulnerability to or severity of foodborne disease.

Some foodborne hazards have been found to be associated with nutrition and development outcomes. However, assessing the impact of these impacts at population scale requires additional efforts in terms of data collection and harmonization of analytical approaches across disciplines. Other factors, such as gender differences, vulnerable groups, and the availability and impact of treatments also warrant further attention by researchers and risk managers.

Key summary findings and considerations relevant to intervention design, within and beyond the EatSafe program, are outlined below.

Recommendations for Intervention Design and Future Studies under EatSafe

This review provides an overview of cross-pathways linking food safety/foodborne illness and nutrition outcomes with focus on health impacts. This body of evidence is meant to support the development of a framework linking food safety and nutrition, as part of Feed the Future and EatSafe programming.
Key findings and considerations include:

- Food safety and nutrition are strongly linked via many impact pathways, in some cases through direct association (e.g. environmental enteropathy is linked to stunting), while in others food safety and nutrition processes may both impact a health outcome (e.g. diabetes or other metabolic processes).
- There is strong evidence that some forms of gastroenteric disease are associated with nutrition outcomes, such as stunting, in children below 5 years old; however, the specific causal mechanisms are still under study. Little evidence is available on adults.
- Since diarrhea and environmental enteropathy are linked to nutrition outcomes in LMICs, but appear to be associated with multiple pathogens, at this stage of data availability interventions aiming to control both FBD burden and associated nutrition impacts may benefit from a broad focus involving multiple pathogens, instead of a more limited focus on few pathogens or pathogen/commodity pairs. However, pathogen-specific studies are needed to understand exposure and attribute burden.
- Physiological mechanisms linking specific foodborne hazard to health and nutrition outcomes are not well characterized, in particular for chronic or time-delayed impacts.
- The connection between a foodborne hazard and major acute health impacts is in most cases established, but data on burden at national and sub-national scale is lacking.
- People purchasing food from informal markets might be more at risk for the cumulative impacts of foodborne disease and associated nutrition impact, including from WASH and housing exposures.
- The incidence and magnitude of impacts linking food safety and nutrition outcomes at total diet and population scale is poorly understood. Even if there is evidence that an impact can occur, its importance at population scale is often unknown.
- The relative magnitude of impacts should be carefully considered when prioritizing interventions. Some well-characterized pathways may not be the most important in terms of population burden.
- Strength of evidence for pathways linking food safety and nutrition is poorly characterized, hindering the ability to prioritize which factors to account for.
- Gender factors are often not included in studies linking food safety and nutrition. Health burden data as well as behavior data, when available, can usually be disaggregated by gender. How other exposure and physiological mechanisms affect genders differently is unclear.
- For some hazards, gendered differences in illness rates may be due to gendered occupational behaviors (e.g. slaughterhouse workers are usually male), not to biological differences. Messaging interventions customized by gender and/or occupation may we warranted.
- Other vulnerable groups, such as pregnant women, the elderly, children, and groups at higher risk of occupational exposure should be considered at potentially higher risk of adverse nutrition outcomes associated with foodborne hazards.
- In light of current evidence gaps, the selection of nutrition outcomes to evaluate and monitor in food safety programs needs further discussion. Recommended actions and outcomes for consideration include: measuring incidence and extent of child development outcomes; fostering increased syndromic surveillance and hazard attribution; including metrics of gut health (as available); including chronic effects of FBD; including measures of hazard-specific impacts on micronutrient status, as appropriate.

6. TABLES

See document for Table 1 (page 11).

Table 2. Foodborne disease with impact on intestinal health, and associated nutrition outcomes

Physiological impact of FBD	Key foodborne hazards, Main physiological mechanisms triggered by hazard	Impact on nutrition-relevant outcomes	Evidence strength	Other impacts, limitations	Ref
Impact of foodborne gastroenteritis					
Secretory diarrhea	Rotavirus, Norovirus, enterotoxigenic *Escherichia coli*, *Vibrio cholerae*, *Giardia lamblia*, *Cryptosporidium parvum*. Affect small intestine: adhere to mucosa, disrupt absorptive and/or enterocytic secretory processes without acute inflammation or mucosal destruction. Many organisms secrete enterotoxins → AMP/cGMP/Ca^{2+} concentration ↑ and target activation → watery diarrhea.	Established links between diarrhea and nutrition outcomes (a)	Meta-analysis of 12 studies of endemic pediatric giardiasis in non-industrialized settings. Lack of attribution of diarrhoea cause to a specific pathogen; true prevalence for	*E. coli*: Post-inflammatory irritable bowel disease (PI-IBS) after infection, pooled prevalence (95%CI): 12% (5–20), 4 prospective studies (1 only exposed subjects). *Cryptosporidium*: Hazard ratio in 12-23 months-olds: 2.3 (95% CI 1.3-4.3); prospective cohort study in 4 African and 3 Asian sites	(59, 76-79)

Secretory diarrhea (cont'd)	*Giardia*: Paradox association with protection from acute pediatric diarrhea, yet ↑ risk of persistent diarrhea.		most agents is unknown.	(9439 moderate-to-severe pediatric diarrhea cases, 13129 controls).	
- Invasive organisms	*Shigella* spp., *Salmonella* spp. Invade intestinal epithelial cells (Shigella), ileum or colon (Salmonella) through chromosomal/plasmic-encoded virulence factors → cell death → apoptosis → release of bacteria and inflammatory mediators. *Campylobacter jejuni* Invade intestinal epithelium, spread to adjacent cells via host invasion receptors, produce nuclease which induces cell cycle arrest and cell damage.	Established links between diarrhea and nutrition outcomes (a)	N/A	Salmonellosis: PI-IBS prevalence after infection 12% (9–15); odds ratio (OR): 5.5 (95% CI 2.3–12.8); Meta-analysis of 3 cohort studies. Shigellosis: PI-IBS prevalence after infection 11% (8–15%); OR: 13.8 (4.2–45.4), 2 prospective studies, 1 study with exposed patients. *Campylobacter spp.*: 12% (10–15%), 3 prospective studies (only exposed), additional data from exposed patients.	(76, 77, 80-82)

Inflammatory diarrhea - Cytotoxin production	Acute inflammatory reaction in the mucosa with various degrees of mucosal ulceration. <u>Enterohemorrhagic *Escherichia coli* (EHEC)</u> 1) Adheres to intestinal villi, activate protein kinase/release Ca^{2+} → ultrastructural changes (villi flattening/dissolution). 2) Produces shiga-like toxins.	Established links between diarrhea and nutrition outcomes (a)	N/A	PI-IBS after infection, pooled prevalence (95% CI) for *C. difficile*: 14% (4–29), 2 prospective, 1 retrospective study.	(76, 77, 79, 83)
	<u>*C. difficile*</u> Toxins adhere to epithelial cells → internalization, activate cascade → disrupt protein synthesis, cell death, inflammation.				
	<u>Enteroaggregative/Enteropathogenic *Escherichia coli* (EAEC/EPEC)</u> Adhere to intestinal brush border: 1) Mucus (biofilm) production 2) Acute inflammatory response: cytokine production, intestinal secretion				

- Hemolytic toxin production	*Listeria monocytogenes* Can resist low pH in stomach, elevated osmolarity, and bile salts. Pathogenesis incompletely understood. Non-invasive (febrile): diarrhea, fever, headache, myalgia. Tropisms may differ between strains.	Established links between diarrhea and nutrition outcomes (a)	N/A	Invasive: penetration of the GI tract, phagocytosis→ internalization→ infections in normally sterile body sites→ replication, intestinal translocation. Mother to fetus transmission.	(70, 84)
Impact of foodborne disease on environmental enteropathy					
Quantitative/ qualitative changes in gut function	Enteroaggregative *Escherichia coli*, *Campylobacter* spp., *Cryptosporidium parvum* - Chronic fecal exposure → qualitative gut microbiota changes; unclear how enteric pathogens trigger the development of environmental enteric dysfunction. - Bacterial overgrowth of small intestine, subclinical bacterial colonization in the upper GI tract	Asymptomatic Enteroaggregative *E. coli* infections → intestinal inflammation → linear growth ↓. Weak associations of enteroaggregative *E. coli* with biomarkers of intestinal inflammation.	1 study in 8 low-resource settings	- Lack of surveillance and clinical case definitions; shift in biomarker distributions in populations with environmental enteropathy impedes individual diagnoses.	(8, 9)
		Campylobacter spp. → markers of permeability ↑, intestinal and systemic inflammation → linear and ponderal growth faltering.	1 study in 8 low-resource settings		

	- Concurrent low-grade inflammation: inhibition of endochondral ossification → inhibition of bone growth. - Potentially reversible villous atrophy, crypt hyperplasia, inflammation, reduced intestinal barrier function.	*Cryptosporidium parvum* excretion associated with growth faltering; unclear mechanism.	1 longitudinal study		
Damage to intestinal tract	<u>Mycotoxins</u> - Damage to intestinal tract ° altered villi: crypt ratio, intestinal absorptive capacity ↓ → zinc deficiency → protein and sphingolipid synthesis Ø; ° enterocyte damage → systemic immune activation. - Intestinal barrier function Ø. - Food intake ↓.	Higher levels of maternal aflatoxin exposure: height-for-age (HAZ) and weight-for age z-scores (WAZ) ↓.	1 longitudinal study	Most evidence from aflatoxin, fumonisin exposure; little evidence for deoxynivalenol and zearalenone, lack of biomarkers.	(17)
		Pediatric fumonisin intake > provisional maximum tolerable daily intake: height and weight ↓.	1 longitudinal study		
Inflammatory damage to the small intestine	<u>*Cryptosporidium, Giardia lamblia*</u> Invasive *Cryptosporidium* infection: inflammatory damage to the small intestine → rapid fluid loss/inability to	Impaired child development, associated with abdominal distension, vomiting, fever and weight loss mostly in children and individuals with HIV/AIDS.	Various studies in LMICs.	Children with poor growth could be at increased risk of Cryptosporidium infection	(59)

Inflammatory damage to the small intestine (cont'd)	absorb micronutrients → growth faltering. Inability to absorb macro-/micro-nutrients during a diarrhoeal episode → disruption of weight and height gain as well as child development.	Chronic *Giardia* infection → weight loss/malabsorption, association with stunting, wasting, and cognitive decline in children in LMICs.	1 study in 8 low-resource settings, 1 longitudinal cohort study.		
		Each diarrhoea episode fom *Cryptosporidium* infection: associated with ↓ HAZ (0·049; 0·014–0·080), WAZ (0·095, 0·055–0·134), and weight-for- height Z score (WHZ) (0·126, 0·057–0·194).	7 studies and 6 individual case study reports.		
		- *Cryptosporidium* infection: significant association with ↓ HAZ (0·030; 0·014–0·045).	Meta-analysis of 6 studies.		
Impact of foodborne disease on nutrient absorption/status					
Physiologic/ histologic GI changes	<u>*Helicobacter pylori*</u> - Change gastric physiology/histology º Iron: limited intestinal absorption (gastric ascorbic acid ↓, gastric juice pH ↑);	*Helicobacter pylori*-infected individuals have ↑ likelihood of, pooled OR (95% CI):		Elevated risk of: - Chronic cholecystitis and cholelithiasis, gestational diabetes mellitus, gastric cancer, systemic sclerosis: moderate evidence.	(27-30)
		- Iron deficiency anemia: 1.72 (1.23–2.42;	14 observational studies		
		- Iron deficiency: 1.33 (1.15–1.54)	30 studies		

Physiologic/histologic GI changes (cont'd)	º Cobalamin malabsorption via: (1) Compromised release of protein-bound dietary cobalamin in the stomach or (2) Gastric atrophy of the corporal mucosa and intrinsic factor deficiency (pernicious anemia). - Virulence factors: *Helicobacter pylori* CagA strains alter host's iron stores; Iron uptake by *H. pylori* may lead to iron deficiency in host - Chronic occult GI blood loss (microbleedings). Risk factors: Low body iron stores, iron deficiency (anemia).			- Hepatic or gastrointestinal illness (e.g. carcinoma/ ulcer, chronic hepatitis C, etc.); neurologic conditions (e.g. Parkinson's disease): low evidence. - Methodological inconsistencies and lack of confounder control in some studies - Metabolic syndrome, type 2 diabetes mellitus - very low evidence.	
		- Anemia: 1.15 (1.00–1.32).	23 studies		
		Following *Helicobacter pylori* eradication + iron therapy vs. iron therapy alone - Ferritin ↑ but not hemoglobin: standardized mean difference (SMD, 95% CI): 0.53 (0.21–0.85) vs. 0.36 (−0.07–0.78).	Meta-analysis of 7 randomised controlled trials (RCTs)		
		- Significant association with: [total random effects of SMD (95% CI)]: º Lower levels of ascorbic acid in plasma: 0.193, (-0.372– -0.015) and gastric juice: -1.087, (1.794–0.379);	15 and 13 studies assessing plasma and gastric juice levels, respectively		
		º Cobalamin: 0.744, (-1.14– -0.340);	14 studies		
		- Association with lower folate levels: -0.433 (-0.943, -0.078), not significant.	9 studies		
		- Positive effect of eradication treatment on ascorbic acid in gastric juice, -1.408 (-2.471, -0.346) and	4 studies and 5 studies, respectively		

		serum cobalamin -1.910; (-3.35, -0.463).			
Intestinal inflammation/ obstruction; internal bleeding	<u>Helminths</u> - Intestinal inflammation and obstruction → impaired nutrient uptake, digestion, and absorption. - Abdominal pain, appetite loss - Internal bleeding → loss of iron → anemia.	Association between helminth infection and serum retinol: SMD (95% CI) -0.30 (-0.48– -0.13); but not with serum ferritin: 0.00 (-0.7–0.7).	Meta-analysis of 9 and 7 observational studies, respectively	Effects of mass deworming for: - Improvement in cognition: little-no effect; high certainty evidence. - Schistosomiasis on growth, short-term attention, cognitive development, school attendance, mortality: little-no effect. No consistent benefits of deworming on indicators of mortality, anemia, growth in children < 5 years or in women of reproductive age.	(23-26)

(a) Clear links between diarrhea and nutrition outcomes (e.g. stunting) (85); no studies were identified which examined nutrition-related outcomes and also attributed the cause of acute gastrointestinal (GI) illness to a specific infectious agent.

Ø, impaired; ↑, increased; ↓, decreased; CI, confidence interval; OR, odds ratio; LAZ, length/height-for-age z-score; WAZ, weight-for-age z-score; WHZ, weight-for height z-score.

Table 3. Foodborne diseases with reproductive health or perinatal growth impacts

Physiological impact of FBD	Key foodborne hazards, Main physiological mechanisms triggered by hazard	Impact on nutrition-relevant outcomes	Evidence strength	Other impacts, limitations	Ref
Changes in glucose metabolism; oxidative/ vessel damage	<u>*Helicobacter pylori*</u> Gestational diabetes mellitus: - Changes in glucose metabolism → chemical changes in the gastric mucosa - ↑ proinflammatory cytokine levels → structural alterations of insulin receptors → inhibition of insulin – receptor interactions Preeclampsia: - Oxidative damage → ↑ lipid peroxidation → endothelial damage → blood pressure ↑. - Indirect vessel damage: activation of clotting cascade or lymphocytes to produce/secrete cytokines in addition to proinflammatory cytokine pathway.	Significant association between *Helicobacter pylori* infection and: - Hyperemesis gravidarum, pooled OR (95% CI): 1.348 (1.156–1.539; P < .001);	Meta-analysis of 38 cross-sectional and case-control studies, 10289 women.	Spontaneous abortion: Inflammatory response in pregnant women ↑ → proinflammatory T-helper 17 cells in the decidua ↑ → foetal stability in utero affected. Significant association between *Helicobacter pylori* infection and: - Spontaneous abortion, OR (95% CI): 1.50 (1.05–2.14; P = 0.024); - Birth defects, OR (95% CI): 1.63 (1.05–2.54; P = 0.03);	(31, 32)
		- Fetal growth restriction: 2.28 (1.21–4.32; P = 0.01);	Meta-analysis of 16 studies.		
		- Gestational diabetes mellitus, 2.03 (1.56–2.64; P < 0.001);	Meta-analysis of reports from 3,697 women.		
		- Low birthweight: 1.59 (1.05–2.40; P = 0.03). - Preeclampsia, OR (95% CI): 2.51 (1.88–3.34; P < 0.001).	8 studies, 12,356 women Meta-analysis of 4630 women		

	Preeclampsia + gestational diabetes mellitus → fetal growth restriction.			Methodological inconsistencies among studies: varying *Helicobacter pylori* detection rate and participant characteristics	
Dehydration/ vomiting, nutrient loss	<u>*Vibrio cholerae*</u> - Severe maternal dehydration → critical hypovolemia → compromised placental/fetal perfusion → fetal hypoxia/acidosis → fetal death. - GI bicarbonate loss → maternal acidosis. - Severe vomiting → Electrolyte changes in amniotic fluid.	Pooled rates (95% CI): - Fetal death: 7.9% (5.3–10.4); no difference by trimester); - Neonatal death: 0.8% (0.0–1.6); - Maternal death: 0.2% (0.0–0.7).	 Meta-analysis of 4 studies. Meta-analysis of 9 studies. Meta-analysis of 9 studies.	No internationally agreed guidelines on the treatment of cholera in pregnancy.	(33, 34)
Environmental enteropathy	<u>Mycotoxins</u> Main suggested pathways in mother and fetus: - Pro-inflammatory cytokines ↑ and/or anti-inflammatory cytokines ↓. - Induction of enteropathy (intestinal inflammation, Ø placental and fetal development).	- Intrauterine fetal growth Ø, promotion of neonatal jaundice; - Perinatal death and preterm birth; - Relationship between gestational aflatoxin exposure and birth weight ↓.	Some evidence Inconclusive No consensus. No meta-analysis: studies used	- Fertility: aflatoxin presence and higher concentrations in semen of infertile men - Liver toxicity + ↑ fetal hemoglobin hemolysis may explain association with neonatal jaundice.	(4, 38)

	- Toxic effects on fetal organs → Ø fetal development.		different effect measures.	Maternal fumonisin exposure potentially associated with hypertensive emergencies in pregnancy or neural tube defects. Limited number of studies, particularly on effects of fusarium mycotoxins.	
Accumulation in fetal organs	<u>Arsenic</u> - Inorganic arsenic crosses the placenta → accumulation in developing fetal organs/ systems - Placental accumulation → disruption and alteration of cord blood methylation.	↑ Risk of - Low birth weight (<2500 grams). - Preterm delivery;	Insufficient: 3 cross-sectional studies from India, outcomes only reported retrospectively.	- Cancer: Skin, liver, kidney bladder, urinary. - Infant mortality/ morbidity/ altered gene/cytokine expression; neurological impairments; impaired intellectual and motor function/ neuropathy; - Coronary/ metabolic illness. No studies on possible paternal effects.	(39-41)

Ø, impaired; ↑, increased; ↓, decreased; CI, confidence interval; OR, odds ratio; LAZ, length/height-for-age z-score; WAZ, weight-for-age z-score; WHZ, weight-for height z-score.

Table 4. Foodborne disease with other nutrition-relevant impacts: cancer, metabolism, and obesity outcomes

Physiological impact of FBD	Key foodborne hazards, Main physiological mechanisms triggered by hazard	Impact on nutrition-relevant outcomes	Evidence strength	Other impacts, limitations	Ref
Foodborne diseases with impact on cancer development					
- Chronic inflammation; Hypochlorhydria; Immunomodulation	<u>*Helicobacter pylori*</u> Peptic ulcerative disease: Infection → gastritis → gastric atrophy and intestinal metaplasia. Gastric cancer: Multiple mechanisms suggested: - Chronic gastric inflammation → precancerous changes of atrophic gastritis and intestinal metaplasia; ↑ risk of gastric cancer. - Chronic *Helicobacter pylori* infection → ↓ gastric acid secretion (hypochlorhydria) →	Infection with iceA1-positive *Helicobacter pylori*: overall 1.26-fold risk - for peptic ulcer (95% CI 1.09–1.45). iceA1 presence significantly associated with peptic ulcer, OR: 1.25 (1.08–1.44). iceA2 presence: inversely associated with peptic ulcer, OR: 0.76 (0.65–0.89). iceA presence: not associated with gastric cancer.	Meta-analysis of 46 studies from 24 countries Sensitivity analysis.	Eosinophile esophagitis: *Helicobacter pylori*-induced immunomodulation: Inverse relationship between *Helicobacter pylori* and eosinophile esophagitis → Indirect evidence (observational studies) lacking direct experimental confirmation. Most evidence available from Asian populations	(47-49)
		Helicobacter pylori eradication → significantly ↓ risk of gastric cancer OR: 0.46 (0.39–0.55).	Limited-moderate evidence that *Helicobacter pylori* eradication ↓ gastric		

	mucosal genetic instability → gastric microbiome growth promotion: processing of dietary components → carcinogens.	Beneficial effect of eradication in Japan, OR: 0.39 (0.31–0.49), particularly among individuals with benign conditions, OR: 0.32 (0.19–0.54).	cancer incidence healthy asymptomatic infected Asians.		
Foodborne diseases with impact on glucose metabolism					
- Autoimmune response	<u>*Toxoplasma gondii*</u> - Infected white blood cells: enhanced migratory feature → facilitated spread in organs; autoimmune process ignition → autoantibody production. - Improved replication in insulin-producing *β*-cells → activation of autoimmunity pathways + inflammation of Langerhans islets → diabetes. - Direct invasion/destruction of pancreatic *β*-cells → pancreatitis and diabetes.	- Type 1 diabetes mellitus: common OR (95% CI, random effects model): 1.10 (0.13–9.57) - Type 2 diabetes mellitus: 2.39 (1.20–4.75). Chronic toxoplasmosis possible risk factor for type 2 diabetes mellitus, but no significant association with type 1 diabetes mellitus.	7 studies	- Limitations of cases-controls studies; Evidence from small studies lacking detail; inconsistent methodology (infection definition). - Production of reactive oxygen species (ROS) and nitric oxide (NO) → reactivation of latent parasite cysts (acute infection). - Inability of neutrophils to perform phagocytosis → response to intracellular pathogens ↓.	(42)

	- Oxidative damage			- Opsonization activity/leukocyte cytotoxicity considerably subsided → susceptibility to opportunistic infections ↑.	
Receptor alteration, oxidative stress	Phtalates (a) Plausible mechanisms: - Alteration of peroxisome proliferator-activated receptors which contribute to adipogenesis, lipid metabolism, and metabolic homeostasis; - Oxidative stress.	Ø Glucose tolerance and blood glucose in pregnancy;	Primary outcomes: number of included studies: - Type 2 diabetes: 1 - Insulin resistance: 3 - Impaired glucose tolerance and blood glucose in pregnancy: 2	- Pregnancy outcomes: Inconsistent evidence of association btw. exposure and time to pregnancy, preterm birth, spontaneous abortion, pregnancy complications. - Obesity: limited evidence (for low molecular weight phthalates) - Thyroid: limited evidence -Limited number of studies. Possible residual confounding by diet.	(43)
		Associations with Type 2 diabetes and: (1) DEHP exposure.	Moderate consistency among studies of insulin resistance, agreement with diabetes study.		
		(2) DBP, DIBP exposure	Moderate evidence, 2 cohorts; strong		

Receptor alteration, oxidative stress (cont'd)			positive associations in the diabetes study, coherent results for insulin resistance.		
		(3) DINP, BBP, DEP exposure	Slight evidence of no association in diabetes study for BBP and DEP.		
Foodborne diseases with impact on thyroid function					
Iodine (I^-) uptake inhibition	<u>Nitrite/nitrate (NO_2^-/ NO_3^-)</u> Inorganic NO_3^-, perchlorate, thiocyanates: I^- uptake inhibition agents → competitive binding to Na^+/ I^- symporter → ↓ I^- bioavailability, ↓ thyroidal I^- stores, ↓ thyroid hormone production → ↓ thyroid stimulating hormone release from pituitary gland.	NO_3^- exposure and thyroid cancer/ hyper-/ hypothyroidism risk	Meta-analysis of seven subgroups of different levels of NO_3^- (n=4) and NO_2^- (n=3).	A WHO report challenges inorganic NO_3^- contribution to endemic goiter: - anti-thyroid effect of NO_3^- mostly observed from drinking water intake, not diet; - NO_3^--induced thyroid dysfunction is likely weak if dietary iodine is available at an adequate range, but may be	
		NO_3^-/NO_2^- exposure and hypothyroidism → OR: 0.98 (0.86, 1.10, P=0.683) and OR: 0.98 (0.79, 1.21, P=0.83), respectively.	No significant associations (Meta-analysis of 3 subgroups of 2 studies)		
		Higher NO_3^- exposure and thyroid cancer risk.	Significant association (risk=1.48; 1.09–2.02,		

Iodine (I) uptake inhibition (cont'd)	Chronic thyroid gland stimulation → change of follicular cells and hypertrophy/hyperplasia induction. Chronic exposure to high NO_3^- levels → hypertrophy, goiter development.		P=0.012; 3 observational studies).	considerable in subjects with nutritional I^- deficiency. Animal studies: high NO_2^-/NO_3^- exposure (~10–600 X acceptable daily intake) → anti-thyroid effects: ↓ thyroid hormone serum levels and histomorphological thyroid gland changes. No similar observations in humans.	
Foodborne diseases with impact on obesity					
Impaired thermogenesis	Persistent organic pollutants (POPs), e.g. DDT, DDE, PCB, phtalates. Underlying mechanisms sparsely studied, one in vivo study suggests ↓ in brown adipose RNA responsible for regulating thermogenesis.	p,p'-DDT and p,p'-Dichlorodiphenyldichloroethylene (p,p'-DDE): "presumed" obesogenic in vivo/in vitro studies.	Moderate (humans)	- Little evidence on role of parent compound vs. congeners. - Urinary measurements may not reflect long-term exposure. - Confounders including diet, use of plastic products, lifestyle factors. - In vivo/in vitro mechanistic studies needed.	(45)
		p,p'-DDT exposure and - adiposity ↑.	Primary in vivo evidence (rodents)		
		Biological plausibility of obesogenic effects of p,p'-DDT and p,p'-DDE. Positive associations between p,p'0-DDE exposure and BMI z-score: b=0:13	Supported by 19 in vivo and 7 in vitro studies		

Impaired thermogenesis (cont'd)	p,p'-Dichlorodiphenyltrichloroethane (p,p'- DDT) exposure → energy expenditure via thermogenesis Ø → energy imbalance → obesity	(0.01–0.25) per log increase of p,p;-DDE.			
		Dose effect for some chemicals (PCB, DDE, phthalates): weight gain at lower doses and weight loss at higher doses. Higher obesity susceptibility upon PCB exposure in girls.	Moderate (human/in vivo /in vitro)		
Increased adipocyte cell differentiation	<u>Bisphenol A</u> Adipocyte cell differentiation ↑ → excess fat accumulation.	Positive correlation between the level of BPA and obesity risk	10 observational studies, 888-4793 participants	Animal models show different obesogenic effects in males and females, limited human evidence.	(46)
		Dose-response: 1-ng/mL BPA increase increased the obesity risk by 11%. Similar results for different types of obesity, gender, and age.			
Steroid hormone receptor agonism/ antagonism	<u>Polychlorinated biphenyls (PCB)</u> Agonist/antagonist of steroid hormone receptors; Induction of specific metabolic pathways	Association between prenatal PCB exposure and:		Lack of adjustment for exposure to other chemicals.	(68)
		Body weight/BMI ↑ at low (<1 ng PCB/mg lipid) exposure; Weight ↓ at high (>4 ng PCB/mg lipid) exposure	2 prospective studies		
		- Pubertal girls: Body size ↑; - Women (20–50 years), children (3–5 years): no association;	5 prospective studies		

		- Girls (4 years): body weight ↓ at intermediate (≥1 – ≤4 ng PCB/mg lipid) exposure			

Ø, impaired; ↑, increased; ↓, decreased; CI, confidence interval; OR, odds ratio; LAZ, length/height-for-age z-score; WAZ, weight-for-age z-score; WHZ, weight-for height z-score

(a) Phthalates considered here include: Di(2-ethylhexyl) phthalate (DEHP), Diisononyl phthalate (DINP), Dibutyl phthalate (DBP), Diisobutyl phthalate (DIBP), Butyl benzyl phthalate (BBP), Diethyl phthalate (DEP).

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APPENDICES

Appendix I. LITERATURE OVERVIEW

Overview of the literature included in this review.

Lead Author	Year	Geography	Population(s)	Specific food(s)	Specific hazard or topic area	Methods
Abba (73)	2009	LMICs, not specified	Children	N/A	Pathogens causing persistent diarrhea	Systematic review
Bahadoran (44)	2015	N/A	Evidence from animal studies, no evidence from human studies	N/A	Nitrite/nitrate	Systematic review
Bloom (40)	2014	Bangladesh, China, India, Taiwan	Pregnant women	N/A	Arsenic	Systematic review
Budge (8)	2019	Low- and middle-income countries, e.g. Bangladesh, The Gambia	Children	N/A	Environmental enteric dysfunction	Review
Cano-Sancho (45)	2017	Belgium, Denmark, Greece, Greenland, Mexico, Poland, Spain, Ukraine, United States	Adults, children	N/A	p, p'-DDT/ p, p'-DDE	Systematic review

Ciglenecki (33)	2013	Haiti	Pregnant women	N/A	*Vibrio cholerae*	Cross-sectional study
Colombara (15)	2018	Global	Children	N/A	Global disability-adjusted life-year estimates of long-term health burden and undernutrition attributable to diarrhoeal diseases	Burden assessment
Dans (56)	2007	Not specified	Children	N/A	Amebic dysentery	Review
Davis (84)	2019	Not specified	N/A	N/A	*Listeria monocytogenes*	Review
de Gier (26)	2014	Bangladesh, Brazil, Cote d'Ivoire, Egypt, India, Indonesia, Kenya, Mauretania Mexico, Nepal, Panama, South Africa, Sri Lanka, Vietnam, Zambia, Zanzibar; urban and rural	School-age children	N/A	Helminths	Systematic review
Eng (82)	2015	Not specified	N/A	N/A	*Salmonella*	Review
European Food Safety Agency - Panel on Biological Hazard (83)	2015	N/A	N/A	N/A	*Escherichia coli*	Technical document

Food and Agriculture Organization, World Health Organization (70)	2004	Not specified	N/A	N/A	*Listeria monocytogenes*	Risk assessment
Ford (47)	2014	China, Colombia, Japan	Adults	N/A	*Helicobacter pylori*	Systematic review
Friedman (75)	2017	Not specified	N/A	N/A	Ciguatera fish poisoning	Review
Gonzales (55)	2019	Bangladesh, Brazil, China, Colombia, India, Indonesia, Iran, Iraq, Mexico, Nigeria, Pakistan, South Africa, Sweden, Turkey	Adults, children	N/A	Antiamebic drugs	Systematic review
Gough (51)	2017	Low- and middle-income countries; not specified	Children	N/A	Antibiotics	Systematic review
Grace (57)	2018	N/A	N/A	N/A	Food safety metrics in LMICs	Review
Grace (62)	2014	Several low- and middle-income countries	N/A	N/A	Food scares	Review
Grace (63)	2015	Cote d'Ivoire, Ethiopia, Ghana, Kenya, Mali, Mozambique, Nigeria,	N/A	N/A	Gender roles	Review

		South Africa, Tanzania, Vietnam				
Grace (57)	2018	N/A	N/A	N/A	Livestock-derived foods during the first 1,000 days of life	Book
Guerrant (13)	2013	N/A	Children	N/A	Diarrhea, stunting	Review
Gulani (25)	2007	Africa, Asia; not specified	Adults, children	N/A	Helminths	Systematic review
Harper (9)	2018	Central and South America, Asia, Africa; half of the studies were conducted in rural locations, 1 study was conducted in both urban and rural populations, 9 studies did not specify the setting	Children, adults	N/A	Environmental enteric dysfunction	Systematic review
Hudak (28)	2017	Argentina, Australia, Bangladesh, Brazil, Bolivia, Canada, China, Cuba, Denmark, Estonia, Ethiopia, Germany, Haiti,	Children, adults, pregnant women, patients	N/A	*Helicobacter pylori*	Systematic review

		India, Israel, Italy, Japan, Korea, Mexico, Netherlands, New Zealand, Portugal, Romania, Sudan, Switzerland, Taiwan, Tanzania, Turkey, UK, USA, Venezuela				
Igwaran (81)	2019	Not specified	N/A - review	N/A	*Campylobacter spp*.	Review
Jaffee (4)	2018	N/A	N/A	N/A	overview	Book
Jones (36)	2003	N/A	N/A	N/A	Congenital toxoplasmosis	Article
Kim (46)	2019	China, India, Italy, Korea, Spain, Thailand, United States	Children	N/A	Bisphenol A	Systematic review
Kirk (71)	2015	Global	N/A	N/A	22 foodborne bacterial, protozoal, and viral diseases	Burden assessment
Kirkpatrick (60)	2002	Haiti	N/A	N/A	Cryptosporidia	Cross-sectional study
Klem (79)	2017	Multiple	N/A	N/A	Irritable bowel syndrome after infectious enteritis	Systematic review

Kotloff (78)	2013	Bangladesh, The Gambia, India, Kenya, Mali, Mozambique, Pakistan	Children with moderate-to-severe diarrhea	N/A	Rotavirus, *Cryptosporidium*, enterotoxigenic *Escherichia coli*, *Shigella, Aeromonas*, *Vibrio cholerae*, *Campylobacter jejuni*	Prospective, multi-center, case-control study
Kyei (38)	2020	The Gambia, Ghana, Kenya, Sierra Leone, Mexico, Nigeria, South Africa Uganda, United Arab Emirates, United States	Pregnant women	N/A	Mycotoxins	Systematic review
Lahner (27)	2012	Not specified	Adults	N/A	*Helicobacter pylori*	Systematic review
Lamont (37)	2011	Not specified	Pregnancy	N/A	*Listeria monocytogenes*	Systematic review
Lanata (12)	2013	Global	Children	N/A	Diarrhea	Disease mortality
Lee (48)	2016	China, Colombia, Finland, Korea, Japan, Taiwan	Adults	N/A	*Helicobacter pylori*	Systematic review
Li (29)	2020	Not specified	Not specified	N/A	*Helicobacter pylori*	Review of systematic reviews
Li (35)	2014	N/A	Pregnancy	N/A	*Toxoplasma gondii*	Systematic review
Lombard (74)	2014	Africa	Children	N/A	Mycotoxin	

Majidiani (42)	2016	Egypt, India, Iran	Not specified	N/A	Toxoplasma	Systematic review
Man (80)	2011	Not specified	N/A - review	N/A	*Campylobacter spp.*	Review
Micha (1)	2020	Global	N/A	N/A	N/A	Global Nutrition Report
Mosites (11)	2017	N/A	Children	N/A	Stunting	Framework
Muhsen (30)	2008	Alaska, India, Turkey, South Korea	Children, adults	N/A	*Helicobacter pylori*	Systematic review
Navaneethan (76)	2008	Not specified	N/A - review	N/A	Infectious diarrhea	Review
Ng (32)	2018	Austria, Bangladesh, Canada, China, Egypt, Greece, Iran, Israel, Japan, Netherlands, Norway, Puerto Rico, USA	Pregnant women	N/A	*Helicobacter pylori*	Systematic review
Oppong (7)	2020	Burkina Faso, Central African Republic, Congo, East Africa, Ethiopia, Gabon, Kenya, Madagascar, Namibia, Nigeria, Senegal, South	Children < 5 years	N/A	Gastroenteritis	Systematic review

		Africa, Tanzania, West Africa				
Petri (18)	2008	Not specified	Children	N/A	Enteric infections, diarrhea	Not part of systematic search, only added for context
Pflughoeft (50)	2012	N/A	N/A	N/A	Microbiome in health and disease	Not part of systematic search, only added for context
Prendergast (14)	2014	Zambia	Children	N/A	Stunting	Not part of systematic search, only added for context
Qekwana (64)	2017	South Africa, urban	Traditional slaughter practitioners	Goat meat	Occupational hazards	Survey
Radke (43)	2019	Belgium, Canada, China, Korea, Mexico, Thailand, United States	Adults, children	N/A	Phthalate	Systematic review
Rahman (39)	2017	Bangladesh, Canada, Romania, United States	Children	N/A	Arsenic	Systematic review
Richard (10)	2013	Bangladesh, Brazil, Peru, Guinea-Bissau	Children ≤ 2 years	N/A	Diarrhea	Review of 7 cohort studies

Rogawski (86)	2017	Bangladesh, India, Nepal, Pakistan, Brazil, Peru, South Africa, Tanzania	Children	N/A	Enteroaggregative *Escherichia coli*	Multicenter study
Rogawski (86)	2017	LMIC	N/A	N/A	Antibiotic exposure	Review
Roesel (65)	2014	Cote d'Ivoire, Ethiopia, Ghana, Kenya, Mali, Mozambique, South Africa, Tanzania	N/A	N/A	Food safety in informal markets	Review
Rytter (58)	2014	N/A	N/A	N/A	Immune system	Review - Not part of search strategy
Sappenfield (69)	2013	N/A	Pregnancy	N/A	Susceptibility to infectious disease	Systematic review
Scharf (85)	2014	Reference to GEMS study in Mali, the Gambia, Kenya, Mozambique, Bangladesh, India, Pakistan; and MAL-ED study in Bangladesh, Brazil, India,	Children	N/A	N/A	Review

		Nepal, Pakistan, Peru, South Africa, Tanzania				
Shirley (66)	2018	Global	N/A	N/A	Amebiasis	Global burden
Smith (17)	2012	Low- and middle-income countries, not specified	Children	N/A	Mycotoxins	Review
Solomons (19)	1993	N/A	N/A	N/A	Gastrointestinal pathogens	Not part of systematic search, only added for context
Squire (59)	2017	Africa	N/A	N/A	*Cryptosporidium, Giardia*	Review
Sugano (49)	2019	China, Colombia, Japan, Korea	Not specified	N/A	*Helicobacter pylori*	Systematic review
Svendsen (67)	2019	Bangladesh, Canada, Croatia, Germany, Italy, New Zealand, Norway, Spain, United Kingdom, United States	Adults, children	N/A	Post-infectious inflammatory bowel syndrome – various pathogens	Systematic review
Syed (16)	2018	Tanzania	Children	N/A	Systemic inflammation	Not part of systematic search, only added for context

Tang-Péronard (68)	2011	Belgium, Canada, Korea, Netherlands, Spain, Sweden, United States	Adults, children	N/A	Chemical hazards	Systematic review
Thiagarajah (77)	2015	Not specified	N/A - review	N/A	Secretory diarrhea	Review
Tran (34)	2015	Haiti, India, Nigeria, Pakistan, Peru, Senegal	Pregnant women	N/A	*Vibrio cholerae*	Systematic review
Troeger (6)	2018	Global	Children < 5 years	Not specified	Disease and nutrition burden	Global disease burden
Welch (24)	2019	China, Bangladesh, Code d'Ivoire, Indonesia, Kenya, Nigeria, Sri Lanka, Tanzania, Philippines, Uganda, Vietnam,	Children in helminth endemic areas	N/A	Helminths	Systematic review
Welch (54)	2017	Not specified	Children	N/A	Deworming	Systematic review
World Health Organization (61)	2009	N/A	Children	N/A	N/A	Training Package
World Health Organization (20-22)	2011 and 2020	N/A	N/A	N/A	Biomarkers of iron and vitamin A status	Not part of systematic search, only added for context

World Health Organization	2015	Global	N/A	N/A	N/A	Global burden of foodborne disease
World Health Organization (41)	2019	N/A	N/A	N/A	Arsenic	Technical document - Not part of systematic search, only added for context
World Health Organization (2)	2019	N/A	N/A	N/A	Preventing disease through healthy environments	Technical document
World Health Organization (23)	2020	N/A	N/A	Helminths	N/A	Factsheet
World Health Organization (53)	N/A	N/A	Children	Helminths	Deworming	Guidance summary
Zhan (31)	2019	China	Pregnant women	N/A	*Helicobacter pylori*	Systematic review

Appendix II. LITERATURE SEARCH STRATEGY

Primary goals:

- Synthesize available evidence in the literature regarding main impact pathways linking food safety or foodborne adverse health outcomes and nutrition outcomes, including biological/ biochemical mechanisms;
- Identify gaps in current food safety literature and research needs.

Search strategy

- If/ where available: evidence from (systematic) reviews and/ or meta-analyses will be reported in lieu of original research articles. Reviews will be identified either through the search strategy (Pubmed and other sources) or through reviewing reference lists of considered articles.
- Primary search in PubMed (s. **Table 1**)
    - Research topics identified from primary research papers in English language from year 2000 onwards.
- Articles cited by reviews will be considered on an individual basis if needed.
- Other considered databases
    - **IFPRI.com / ICRISAT.org** – Key word: '*Food safety*'
    - **Worldbank.com** – Key word: "*Food safety*"
    - **WHO.org** – Health topics: 'Food Safety' à '*Areas of work*'
        - Antimicrobial resistance in the food chain
        - Chemical risks
        - Foodborne diseases
        - Food hygiene
        - Food technologies
        - International Network of Food Safety Authorities (INFOSAN)
        - Microbiological risks
        - Nutrition and food security
        - Zoonoses and the environment

      Screening of all titles and potentially relevant abstracts from 'List of Publications' in each area.
    - **CGIAR.org** / **CIAT.CGIAR.org** – Screen all titles and potentially relevant abstracts of entire publication list ('*Research*' à '*Publications*')
    - **CYMMIT.org** – '*Resources'* à '*Publications*'- Key word: '*Food safety*'

- **FAO.org** – Screen titles and abstracts of all publications in '*Food safety & quality*' à '*Resources*'
- **Worldfishcenter.org** – Key word: '*Food safety*'

- Screening of '*Reference*' lists of identified relevant articles à Screening of abstracts for potentially relevant titles.

Screening process for all retrieved articles

Decision process: Title screening > Abstract screening > Fulltext screening > In-/ exclusion

In the screening process, the reviewer(s) will look for keywords as indicated in the PubMed search strategy.

1) Title screening
   - Include: Titles indicating to cover aspects of both food safety and nutrition.
   - Exclude: Titles that are obviously not within the scope of the project.

     In case of doubt, move article to abstract review.

2) Abstract screening for potentially relevant titles.

   Include if abstract appears to be of interest for the review, otherwise exclude.

3) Fulltext screening for all titles remaining after title and abstract screening.
   a. Include if abstract appears to be of interest for the review. Make note in case the general topic is already extensively covered by a (systematic) review.
   b. Reference lists of relevant articles will be screened and potentially relevant references will be screened according to steps 2) and 3).

Data extraction

Data will be extracted for included articles (see Excel spreadsheet).

Reporting

Information deemed most relevant by the reviewer(s) will be included in tables and/or text.

PubMed search

#	Search string	# of results	Concept
1	Food Safety[MeSH Terms] or Food Safe*[tiab] or Safe Food*[tiab] or Unsanitary Food*[tiab] or Insanitary Food*[tiab] or Sanitary Food*[tiab] or Food-Safe*[tiab] or Food-Safety-Hazard*[tiab] or Food Contaminat*[tiab] or Unsanitary Feed*[tiab] or Insanitary Feed*[tiab] or Sanitary Feed*[tiab] or Foodborn*[tiab] or Food-born*[tiab] or Food born*[tiab] or Spoil*[tiab] or Food Hygien*[tiab] or Hygienic Food*[tiab] or Hygienic Practic*[tiab] or Hygiene-Food*[tiab] or Hygiene-Practic*[tiab] or Biological Hazard*[tiab] or Chemical Hazard*[tiab] or Physical Hazard*[tiab] or Food Hazard*[tiab] or Hazardous Food*[tiab] or Allergenic Hazard*[tiab] or Biological-Hazard*[tiab] or Chemical-Hazard*[tiab] or Physical-Hazard*[tiab] or Allergenic-Hazard*[tiab] or Food Pathogen*[tiab] or Pathogen in Food*[tiab] or Pathogens in Food*[tiab] or Foodborne zoono*[tiab] or Food-borne zoono*[tiab] or Food poison*[tiab] or Food-poison*[tiab] or Poisonous food*[tiab] or food handl*[tiab] or food-handl*[tiab] or Virus-commodit*[tiab] or food-borne-vir*[tiab] or Viruscommodit*[tiab] or FBD*[tiab] or impur*[tiab]	130032	Food safety [Mesh] and [tiab] terms MeSH = **Medical** Subject Headings, this should include most relevant terms related to food safety.
2	Nutritional Status[MeSH Terms] or Malnutrition[MeSH Terms] or Diet, Food, and Nutrition[MeSH Terms] or Food*[tiab] or Nutritio*[tiab] or Eat*[tiab] or Drink*[tiab] or Foodstuff*[tiab] or Food-stuff*[tiab] or Aliment*[tiab] or Cook*[tiab] or Snack*[tiab] or Cuisine*[tiab] or Kitch*[tiab] or Meal*[tiab] or Nourish*[tiab] or Diet*[tiab] or Consum*[tiab] or Food Prepar*[tiab] or Stunted Growth*[tiab] or Underweight*[tiab] or Stunt*[tiab] or Wasted*[tiab] or Wasting*[tiab] or Thinness*[tiab] or micronutrient deficien*[tiab] or nutrient deficien*[tiab] or hidden hunger*[tiab] or hidden-hunger*[tiab] or hunger*[tiab] or double-burden*[tiab] or double burden*[tiab] or Malnutri*[tiab] or Malnour*[tiab]	2183450	Nutritional status [Mesh] and tiab terms MeSH term

3	LMIC*[tiab] or Low-income*[tiab] or Middle-income*[tiab] or Income*[tiab] or Low- and Middle-Income Countr*[tiab] or Low and Middle-Income Countr*[tiab] or Developing Countr*[tiab] or Developing nation*[tiab] or Rural*[tiab] or Remote*[tiab] or Less developed countr*[tiab] or Least developed countr*[tiab] or Under developed countr*[tiab] or Least developed populat*[tiab] or Under developed populat*[tiab] or Least developed nation*[tiab] or Under developed nation*[tiab] or Resource limit*[tiab] or Resource poor*[tiab] or Third World*[tiab] or Third-World*[tiab] or Developing-Countr*[tiab] or Developing-nation*[tiab] or Less-developed countr*[tiab] or Least-developed countr*[tiab] or Under-developed countr*[tiab] or Least-developed populat*[tiab] or Under-developed populat*[tiab] or Least-developed nation*[tiab] or Under-developed nation*[tiab] or Resource-limit*[tiab] or Resource-poor*[tiab] or Afri*[tiab] or Sahara*[tiab] or sub-sahara*[tiab] or Asia*[tiab] or Latino*[tiab] or Latina*[tiab] or Latin Americ*[tiab] or Latin-Americ*[tiab] or South America*[tiab] South-America*[tiab] or Carib*[tiab] or Carrib*[tiab] or Afghani*[tiab] or Albania*[tiab] or Algeria*[tiab] or Algier*[tiab] or Angola*[tiab] or Antigua*[tiab] or Argentin*[tiab] or Armenia*[tiab] or Azerbaijan*[tiab] or Bangladesh*[tiab] or Belarus*[tiab] or Beliz*[tiab] or Benin*[tiab] or Bhutan*[tiab] or Bolivia*[tiab] or Bosnia* and Herzegovina*[tiab] or Bosnia*[tiab] or Botswan*[tiab] or Batswan*[tiab] or Tswan*[tiab] or Brazil*[tiab] or Brasil*[tiab] or Burkina Faso*[tiab] or Burundi*[tiab] or Cabo *[tiab] or Cambodia*[tiab] or Cameroon*[tiab] or Central Africa*[tiab] or Chad*[tiab] or China*[tiab] or Chine*[tiab] or Chino*[tiab] or Colombia*[tiab] or Comoro*[tiab] or Congo*[tiab] or Cook Island*[tiab] or Costa Rica*[tiab] or Côte d'Ivoir*[tiab] or Ivori* Cuba*[tiab] or Djibouti*[tiab] or Dominica*[tiab] or Dominican Republic*[tiab] or Ecuador*[tiab] or Egypt*[tiab] or El Salvador*[tiab] or Equatorial Guinea*[tiab] or Eritrea*[tiab] or Ethiopia*[tiab] or Fiji*[tiab] or Gabon*[tiab] or Gambia*[tiab] or	1320101	LMIC [tiab] terms

	Georgia*[tiab] or Ghana*[tiab] or Grenada*[tiab] or Guam*[tiab] or Guatemala*[tiab] or Guinea*[tiab] or Guyana*[tiab] or Haiti*[tiab] or Hondura*[tiab] or India*[tiab] or Indonesia*[tiab] or Iran*[tiab] or Iraq*[tiab] or Jamaica*[tiab] or Jordan*[tiab] or Kazakh*[tiab] or Kenya*[tiab] or Kenia*[tiab] Kiribat*[tiab] or Korea*[tiab] or Kosov*[tiab] or Kyrgy*[tiab] or Lao*[tiab] or Leban*[tiab] or Liban*[tiab] or Lesotho*[tiab] or Liberia*[tiab] or Libya*[tiab] or Lybia*[tiab] or Macedoni*[tiab] or Madagas*[tiab] or Malawi*[tiab] or Malaysia*[tiab] or Maldiv*[tiab] or Mali*[tiab] or Marian*[tiab] or Marshall*[tiab] or Maurit*[tiab] or Mexic*[tiab] or Micrones*[tiab] or Moldo*[tiab] or Mongol*[tiab] or Montenegr*[tiab] or Montserrat*[tiab] or Morocc*[tiab] or Mozambiqu*[tiab] or Myanmar*[tiab] or Burme*[tiab] or Democratic Republic*[tiab] or Democratic-Republic*[tiab] or Republic*[tiab] or Burma*[tiab] or Namibia*[tiab] or Nauru*[tiab] or Nepal*[tiab] or Nicaragua*[tiab] or Niger*[tiab] or Nigeria*[tiab] or Niue*[tiab] or Pakistan*[tiab] or Palau*[tiab] or Panam*[tiab] or Paraguay*[tiab] or Peru*[tiab] or Philippi*[tiab] or Philipi*[tiab] or Puerto*[tiab] or Rwand*[tiab] or Ruand*[tiab] or Saint*[tiab] or Samo*[tiab] or São Tom*[tiab] or Sao Tom*[tiab] or Senegal*[tiab] or Serbi*[tiab] or Sierra Leon*[tiab] or Sierra-Leon*[tiab] or Solomon*[tiab] or Somali*[tiab] or South Africa*[tiab] or South Sudan*[tiab] or Sri Lank*[tiab] or Sri-Lank*[tiab] or Sudan*[tiab] or Surinam*[tiab] or Swaziland*[tiab] or Syria*[tiab] or Tajikistan*[tiab] or Tanzania*[tiab] or Thai*[tiab] or Timor *[tiab] or Togo*[tiab] or Tokelau*[tiab] or Tonga*[tiab] or Tunisia*[tiab] or Turk*[tiab] or Turkmeni*[tiab] or Tuvalu*[tiab] or Uganda*[tiab] or Ukrain*[tiab] or Uzbek*[tiab] or Vanuat*[tiab] or Venezuel*[tiab] or Vietnam*[tiab] or Virgin*[tiab] or Wallis*[tiab] or West Bank*[tiab] or West-Bank*[tiab] or Gaza*[tiab] or Ghaza*[tiab] or Palestin*[tiab] or Palaestin*[tiab] or Yemen*[tiab] or Zambia*[tiab] or Sambia*[tiab] or Zimbab*[tiab] or Simbab*[tiab]		

	or Middle East*[tiab] or Middle-East*[tiab] or Health Development Inde*[tiab] or Ngwa*[tiab] or Development Inde*[tiab] or Austrones*[tiab] or Ceylon*[tiab] or Hong Kong*[tiab] or Taiwan*[tiab] or Poor household*[tiab] or Disadvantaged nation*[tiab] or Poor nation*[tiab] or Disadvantaged household*[tiab] or Poor societ*[tiab] or Disadvantaged societ*[tiab] or Poor count*[tiab] or disadvantaged count*[tiab] or vulnerable nation*[tiab] or vulnerable household*[tiab] or vulnerable societ*[tiab] or Poor econom*[tiab] or disadvantaged econom*[tiab] or vulnerable econom*[tiab] or Low- and Middle-Income Econom*[tiab] or Low and Middle-Income Econom*[tiab] or Developing Econom*[tiab] or Less developed Econom*[tiab] or Least developed Econom*[tiab] or Under developed Econom*[tiab]		
4	#1 AND #2 AND #3 **Note:** Only articles from the combined search (#4) were screened.	8323	Combination