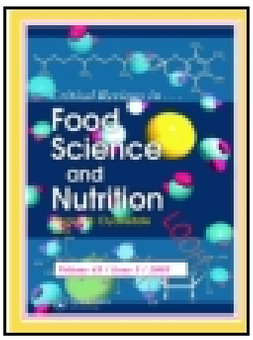

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Dietary mycotoxins exposure and child growth, immune system, morbidity, and mortality: a systematic literature review

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REVIEW

Dietary mycotoxins exposure and child growth, immune system, morbidity, and mortality: a systematic literature review

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ABSTRACT

The aim of this study was to systematically review associations between dietary mycotoxins exposure and child growth and morbidity of children aged 5 years or younger. Peer-reviewed literature was searched in MEDLINE, EMBASE, COCHRANE, CINAHL, Web of Science, and PsycINFO. Experimental and observational studies were considered. The exposures were dietary mycotoxins during pregnancy, lactation and childhood, and mycotoxins concentrations in the diet, breast milk, urine, and blood. From a total of 4869 references, 86 full-text papers were extracted of which 50 were included in this review. The methodological quality and risk of bias were evaluated and quality of the collective evidence was assessed using GRADE. Uncertainty remains whether mycotoxins exposure affects child growth, immunity and mortality and the overall quality of the evidence is very low. Overall however, we cannot rule out a possible association between dietary mycotoxins, in particular, AF and FUM and child malnutrition. Our analyses were limited by the reporting quality, difference in findings, heterogeneity of outcomes, mycotoxins detection methods, and the observational nature of most studies. Robust study designs with adequate sample size, use of validated biomarkers of exposure and assessment of co-occurrence of mycotoxins and their synergistic effects are required to provide the further evidence regarding a potential effect of dietary mycotoxins exposure on child growth and immunity.

KEYWORDS

Aflatoxin; child growth; diet; mycotoxin exposure; systematic review

Introduction

Many agricultural products, especially those rich in carbohydrates, are attractive colonization sites for fungi. Mycotoxins are toxic secondary metabolites of fungal growth, and are found to contaminate agricultural products (Chelkowski 1998). The contamination by mycotoxins can occur during pre-harvest at the farm level, after harvest handling, storage, and food processing. Among many mycotoxins, aflatoxins (AF) and fumonisins (FUM), are widespread in major cash-crops, agricultural commodities and their products, in particular in low-and-middle-income countries (Wild and Gong 2009). AF are highly carcinogenic, exert hepatocellular damage and can cause death in both humans and animals (International Agency for Research on Cancer 1993). Outbreaks of high AF exposure have resulted in many casualties (Azziz-Baumgartner et al. 2005).

Consumption of mycotoxins may result in impaired immunity and decreased resistance to infectious diseases (Bondy and Pestka 2000; Turner et al. 2003). Morbidity and child growth are interrelated, and may influence the health and survival of children under five years of age. The suggested pathways through which mycotoxins lead to growth retardation are inhibition of protein synthesis (i.e. for AF, deoxynivalenol (DON), increase in systemic cytokines (for DON), and/or inhibition of ceramide synthase (for FUM (Bouhet and Oswald 2007)). Inhibition of protein synthesis can result in physical alterations to the intestine, leading to malabsorption of nutrients and impaired intestinal barrier function similar to the pathology in environmental enteropathy (Smith, Stoltzfus, and Prendergast 2012).

Dietary exposure to high levels of aflatoxins during pregnancy is highly prevalent in low- and middle income countries, and are considered as a potential contributor to fetal growth restriction and childhood stunting (Turner et al. 2007; Shuaib et al. 2010; Piekkola 2012; Castelino et al. 2014).

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Dietary exposure to AF in childhood occurs mainly through complementary infant foods and carry-over via breast milk (Magoha et al. 2014). Even though several studies have shown a potential correlation between mycotoxins exposure and childhood stunting, the collective evidence has not been assessed. A previous study (Chen, Riley, and Wu 2018) reviewed dietary FUM and growth impairment in children and animals. However, this study was focused on a single mycotoxin (FUM), while co-occurrence of mycotoxins and the subsequent multi-contamination risk exposure is widely reported.

In addition, current regulations use toxicological data taking into account single mycotoxin exposure at a time, and do not consider the combined effects of mycotoxin (Smith et al. 2016). The present systematic review summarized available evidence from experimental, cohort, case–control and analytical cross-sectional studies regarding dietary mycotoxins exposure and its associations with growth, immune system, morbidity and mortality of children aged 5 years or younger.

Methods

The protocol for this systematic review was registered in PROSPERO https://www.crd.york.ac.uk/prospero/ with registration number CRD42018082046.

Criteria for considering studies for this review

Types of studies

This review considered both experimental and observational study designs including randomized controlled trials (RCTs), non-randomized controlled trials, quasi-experimental studies, before and after studies, prospective and retrospective cohort studies, case–control studies and analytical cross-sectional studies.

Population

This review considered all studies involving children aged 5 years or younger (0–59 months), published in English or French. We did not find a study from other languages other than English.

Types of exposure

Mycotoxin exposure during pregnancy, lactation and childhood, and also mycotoxin in the diet, breast milk, urine and blood were considered.

Outcomes

This review considered studies that include the following outcome measures:

- Child growth. Child growth is an indicator of nutritional status and health in populations and is measured by anthropometric measurements, such as weight for length/height, weight for age, length/height for age, mid-upper arm circumference (MUAC) and head circumference. The term malnutrition addresses three broad groups of conditions: undernutrition, which includes wasting (low weight-for-height), stunting (low height-for-age) and underweight (low weight-for-age). These indicators are used to measure nutritional imbalance resulting in undernutrition (assessed from underweight, wasting and stunting). Underweight: weight for age < -2 standard deviations (SD), stunting: height for age < -2 SD and wasting: weight for height < -2 SD of the WHO Child Growth Standards median (UNICEF 2013). Low birth weight (LBW): LBW is defined as a weight of less than 2500 grams at birth.
- Morbidity: hepatic, gastrointestinal and respiratory diseases and marasmus, kwashiorkor and marasmic-kwashiorkor.
- Deaths occurring for children under five years of age: perinatal mortality, neonatal mortality, infant mortality, and child mortality.
- Studies on immune system of children under-five years of age. Various biological biomarkers of immune system, such as lymphocytes, cytokines and immunoglobulin have been used to examine immune system status of children. Immunomodulatory effects primarily as immunosuppression of cell-mediated immunity and Impairment of phagocytic cell function.

Studies were reviewed regardless of year of publication, and there were no restrictions with regard to setting or country.

Study exclusion criteria

Animal studies, drug trials, diagnostic trials, case reports or studies only reporting qualitative findings were not considered.

Information sources

The search was first completed on December 9, 2017 and was updated in October 2018. The databases included: MEDLINE, EMBASE, COCHRANE LIBRARY, CINAHL, Web of Science, PsycINFO, gray literature and conference abstracts through Google Scholar, and reference lists to the papers reviewed. We also searched the clinical trials registry at ClinicalTrials.gov (www.clinicaltrials.gov). After a screening of titles and abstracts retrieved, full texts were examined in detail and screened for eligibility. Reference lists of eligible studies were searched by hand for additional articles.

Search strategy

We developed a search strategy in PubMed for MEDLINE (as described below) from a previous study (Dangour et al. 2013), and adapted it as required for other electronic databases. The search syntax for all databases is included in Supplementary material S1 Appendix.

((((((Child*[tiab] OR Newborn[tiab] OR newborns[tiab] OR neonate[tiab] OR neonates[tiab] OR neonatal[tiab] OR

infant[mh] OR infant[tiab] OR infants[tiab] OR child, preschool[mh] OR preschool[tiab] OR "pre school"[tiab] OR toddler[tiab] OR toddlers[tiab] OR Pediatrics[tiab] OR pediatric[tiab] OR paediatric[tiab] OR "young children" [tiab] OR "under five years"[tiab] OR "under 5 years" [tiab] OR utero[tiab] OR fetal[tiab])))) AND ((Mycotoxins[mh] OR mycotoxin*[tiab] OR aflatoxin[tiab] OR aflatoxins[tiab] OR aflatoxins[mh] OR aspergillus[tiab] OR fumonisin[tiab] OR fumonisins[tiab] OR zearalenone[tiab] OR deoxynivalenol [tiab] OR ochratoxin[tiab] OR fusarium[tiab] OR Patulin[tiab] OR citrinin[tiab] OR "ergot alkaloids" [tiab] OR trichothecene[tiab]))) AND ((((((Growth[tiab] OR Stunting[tiab] OR stunted[tiab] OR wasted[tiab] OR wasting[tiab] OR underweight[tiab] OR short stature[tiab] OR malnutrition[mh] OR malnutrition[tiab] OR malnourished [tiab] OR "mid upper arm circumference"[tiab] OR mid-upper arm circumference[tiab] OR "MUAC"[tiab] OR "linear growth"[tiab] OR "growth faltering"[tiab] OR "childhood stunting" [tiab] OR "growth impairment" [tiab] OR "growth retardation" [tiab] OR "growth deficit" [tiab] OR "child growth" [tiab] OR "growth restricted" [tiab] OR birthweight[tiab] OR "birth weight" [tiab] OR length-for-age [tiab] OR height-for-age [tiab] OR weight-for-height [tiab] OR weight-for-age [tiab] OR emaciated [tiab] OR thin[tiab] OR protein-energy malnutrition[tiab])))) OR ((immune system[mh] OR immune system[tiab] OR immunity [mh] OR immune status[tiab] OR antibody[tiab] OR enteropathy[tiab] OR immunosuppression[tiab] OR immunodeficiency[tiab] OR immunomodulation[tiab] OR immunoglobulin[tiab] OR immunotoxin[tiab] OR immunocompromising[tiab])))) OR ((Morbidity[tiab] OR Infections OR jaundice[tw] OR hepatitis[tiab] OR outbreak[tiab] OR marasmus[tiab] OR kwashiorkor[tiab] OR "marasmic kwashiorkor"[tiab])))) OR ((Child mortality[mh] OR mortality[tiab] OR death[tiab] OR "postnatal mortality" [tiab] OR "infant mortality" [mh] OR "neonatal mortality" [tiab] OR "perinatal death"[mh] OR "postnatal death" [tiab])))))) NOT ((animals[mh]) NOT humans[mh])

Data management

EndNote software was used to manage the references and to identify duplicates. Articles were exported directly from the search database and categorized in EndNote to facilitate review and data extraction.

Selection process

KT performed the initial title screening. Next, abstracts of the retrieved records were screened independently by two reviewers (KT and MDB) to assess eligibility. The full-text of eligible studies were assessed by three independent reviewers (KT, MDB, and CL) to determine final inclusion in the review. If no agreement was reached, an additional review author (PK) was asked to make an independent assessment.

Data collection process

Data were extracted from manuscripts using a template designed for this review. We piloted the data collection form in a few studies and modifications were made where necessary. The data extraction included specific details about the author and year of publication, interventions/exposure, study population, study methods and designs, study setting, sample size, outcome measurement, exposure measurement method, biomarkers of effect and exposure, outcomes of significance to the review question and specific objectives. Where necessary, we tried to contact the corresponding authors of primary studies to obtain missing information.

Assessment of study quality and risk of bias

We used the GRADE (Grading of Recommendations Assessment, Development and Evaluation) system (Guyatt et al. 2009) to assess the quality of evidence for all the outcomes consistently. The methodological quality and bias of epidemiological studies were evaluated using the Newcastle-Ottawa scale (NOS) for observational studies (Wells 2013). Each study was appraised for items, categorized in three groups: the selection of the study groups, the comparability of the groups, and the exposure and the outcome of interest. The NOS score ranges from zero to nine. The Cochrane methodology was used to assess the risk of bias for intervention studies (Higgins and Altman 2008). The quality (risk of bias) for each study was independently assessed by two reviewers (KT and AM). Discrepant scores were resolved by discussion with a third reviewer (PK). Studies were not excluded on the risk of bias grounds.

Synthesis

Given the diversity of studies, we did not conduct a meta-analysis for pooled estimates. However, we addressed heterogeneity qualitatively due to differences in study design, variation in the way in which confounding is considered in the analysis and risk of other types of biases associated with the study design.

A narrative synthesis of studies was performed, including a structured summary and discussion of the studies' characteristics and findings. This systematic review was reported in accordance with the PRISMA statement (Moher et al. 2009).

Results

Study selection

The database search identified 4869 references as shown in Figure 1. A total of 3,274 references remained in the database after duplicates were removed. We found an additional nine references through hand searching of relevant articles. We considered 86 full-text papers for inclusion in this review, of which 50 met our inclusion criteria.

The findings of this review are presented in the following sequence for each outcome of interest; description of studies and quality assessment, results from the different studies and strength of evidence. We organized the findings by

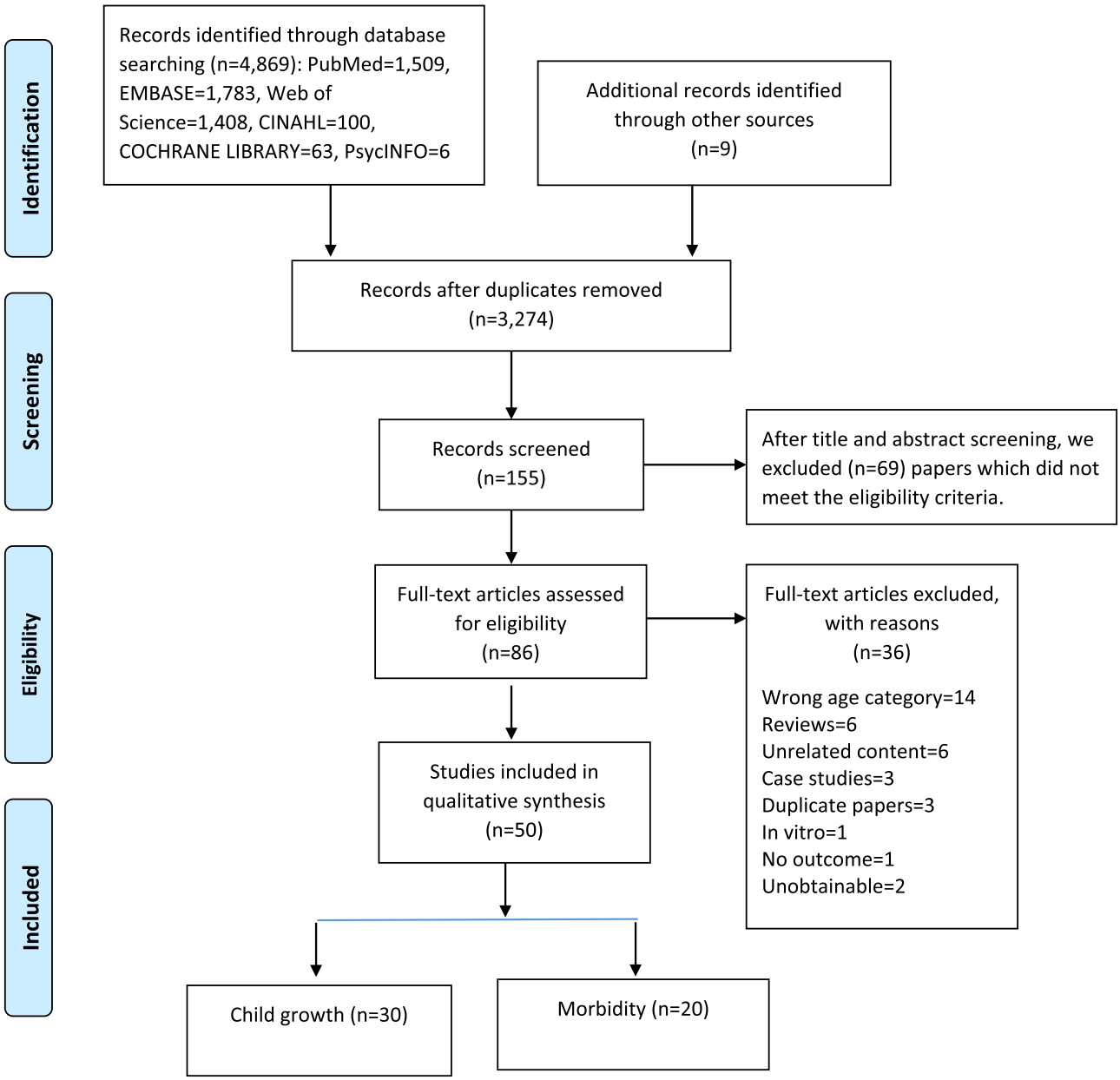

Figure 1. Study flow diagram.

study design, by the strength of evidence i.e. from RCTs, longitudinal, case–control to cross-sectional studies.

Mycotoxins exposure and child growth

Description of included studies

Studies took place mostly in Africa (77.3%), Asia (9.1%), North America (4.6%) and the Middle East (9.1%). The studies were published between 2002 and 2018. The studies were observational: cross-sectional studies ($n = 9$; 45%), and prospective cohort studies ($n = 11$; 55%). The included cohort studies had follow-up periods ranging from 5 months to 36 months. Two studies were cluster RCTs (Hoffmann, Jones, and Leroy 2018; Kamala et al. 2018). Risk of bias was found to be high in (Kamala et al. 2018) and low in (Hoffmann, Jones, and Leroy 2018). We were unable to find the full-text of two studies (Natamba 2016; Mahfuz 2017) and included the abstracts in the present review. Omission of these abstracts did not alter the outcome of the present review. Table 1 provides full study characteristics and scores on the NOS in Supplementary material Appendix S2). Only four cohort studies received seven out of the maximum nine scores. The cohort studies did not clearly report whether they had ascertained the outcomes of interest (child growth) at the beginning of the studies. There was an inappropriate selection of exposed and unexposed in cohort studies from different populations.

Mycotoxins exposure and child growth

Associations with child growth were only reported for AF and FUM. All the studies assessed the association with dietary mycotoxins and stunting. Wasting, underweight, MUAC,

Table 1. Summary of studies on the association between mycotoxins exposure and child growth.

Author/year	Study setting/ study population	Study design	Detection rate (%)	Mycotoxin type	Technique	Matrix/type of food	Outcome measurement	Adjustment for covariates	Findings	Quality score
(Hoffmann, Jones, and Leroy 2018)	Kenya 881 children up to 2 years of age	Cluster randomized controlled trial	With 100 % detection rate. The mean level of serum AFB1-lysine adduct was 18.1 pg/mg albumin (median 6.1 pg/mg albumin)	AF	HPLC-FD	AFB1-lys	LAZ Prevalence of stunting	Socioeconomic, age, season, maternal height and education.	The intervention had no effect on child LAZ or on the prevalence of stunting but had a significant effect on ln serum AFB1-lysine adduct levels at end line (24 months). However, a significant effect on child linear growth was found at midline (11 to 19 months)	Low risk of bias
(Kamala et al. 2018)	Tanzania 300 children	Cluster randomized controlled trial	NR	AF and FUM	HPLC	Maize	WAZ, dietary assessment	Mother's education level	AFs and FUMs intake were inversely associated with WAZ. Prevalence of WAZ was 6.7% lower in the intervention group. Mean WAZ difference between the groups was 0.57 (95% CI; 0.16 to −0.98; $p = 0.007$).	High risk of bias
(Gong et al. 2004)	Benin 200 children (16-37 months of age) 8 months follow up (February, June, and October)	Longitudinal	GM pg/mg: 37.4, 38,7, and 86,8 in February, June, and October respectively.	AF	ELISA	AF-alb	Measured height, age, weight. WHZ, WAZ and HAZ	Age, socio-economic status, micronutrients, and weaning status	AF-alb was inversely associated with HAZ but not with WHZ scores and WAZ score. There was a strong negative correlation between AF-alb and height increase over the 8 months' follow-up.	6
(Turner et al. 2007)	Gambia 138 children 14 months follow-up from birth until one year of age.	Longitudinal	GM pg/mg (range): 40.4 pg/mg (4.8–260.8 pg/mg), 10.1 pg/mg (5.0–189.6 pg/mg) and 8.7 pg/mg (5.0–30.2 pg/mg) in maternal, cord and infant blood, respectively.	AF	ELISA	AF-alb	Weight, height, age, WAZ and HAZ	Age, gestation time, season	High maternal AF-alb was strongly related to a lower level of weight-for-age and height-for-age in the Gambian infants. AF-alb at Week 16 was significantly negatively related to HAZ (−0.558 SD; $p = 0.002$), but not WAZ. A reduction of maternal AF-alb from 110 pg/mg to 10 pg/mg would lead to a 0.8 kg increase in weight and 2cm increase in height within the first year of life.	6
(Kimanya et al. 2010)	Tanzania 215 infants (6 months follow-up at 6 and 12 months of age)	Longitudinal	FUMs at levels varying from 21 to 3201 μg/kg.	FUM	HPLC	Maize	Measured Age, length and weight.	Age, energy and protein intake	Children who consumed complementary food with FUMs concentrations > 2μg/kg bw/day were significantly shorter on average by 1.3 cm ($\beta = -1.374$, $p = 0.002$) and 328 g lighter at 12 months ($\beta = -0.328$, $p = 0.002$).	7

(*continued*)

Table 1. Continued.

Author/year	Study setting/ study population	Study design	Detection rate (%)	Mycotoxin type	Technique	Matrix/type of food	Outcome measurement	Adjustment for covariates	Findings	Quality score
(Magoha et al. 2014)	Tanzania 143 infants Three follow-ups (1st, 3rd and 5th months of age)	Longitudinal	AFM1 at levels ranging from 0.01 to 0.55 ng/ml.	AF	HPLC	AFM1 (breast milk)	At 1st month/143: HAZ(11%), WAZ(4%), WHZ(4%): 3rd months/ 121: HAZ(13%), WAZ(9%), WHZ(1%): 5th months/ 118: HAZ(17%), WAZ(10%), WHZ(3%):	Age, education of the mother, earnings of the mother, dietary diversity score	A small but significant inverse association was observed between AFM1 exposure levels and WAZ or HAZ.	6
(Natamba 2016)	Uganda 246 dyads (Follow-up: pregnancy up to one year)	Longitudinal	Mean maternal serum AFB1 113.9 (±100.6) pg/mg	AF	NA	Maternal serum	WAZ, HAZ, WHZ	Prenatal food insecurity, dietary diversity, asset index, and infant age	AF exposure negatively affect infant linear growth (HAZ) in HIV (+) pregnant women and their HIV-exposed infants. Infants of HIV (+) women in the high perinatal AF category had 0.460 lower HAZ scores than infants of HIV (−) women in the low AF exposure category ($p = 0.006$).	NA
(Mitchell et al. 2017)	Nepal 85 children Three follow-up (at 15, 24 and 36 months of age)	Longitudinal	GM pg/mg: 3.62	AF	UPLC	AFB1-lys	Measured age, LAZ (19%), WAZ and WLZ	Age, weaning age, weaning status, mother's education level, vitamin A plasma concentrations, consumption of grains, energy-adjusted iron and zinc consumption.	The chronic AF exposure in this cohort was not significantly associated with anthropometric *z*-scores.	8
(Mahfuz 2017)	Bangladesh 744 children birth to 36 months follow-up	Longitudinal	GM 1.07 pg/mg (0.04-123.5)	AF	NA	AFB1-lys	WAZ, HAZ, WHZ	Breastfeeding, dietary intake, seasonal variation	No association was detected between anthropometric indices and AF exposure	NA
(Leroy et al. 2018)	Southern Mexico 347 children (10 months follow-up)	Longitudinal	Detection rate of 99.4%	AF	HPLC	AFB1-lys	HAZ, HAD	Household socioeconomic status, and child's diet.	AF exposure was associated with greater linear growth.	7
(Shirima et al. 2015)	Tanzania 166 children (6-14 months old).	Longitudinal	AF-alb GM pg/mg (detection %): 4.7 (67%), 12.9 (84%) and 23.5 (99%) at recruitment, 6	AF and FUM	HPLC-MS	AF-alb (UFB1)	At recruitment LAZ(44%), WAZ(8%), WLZ(2%): 6 months: LAZ(55%),	Breastfeeding, maternal education, socioeconomic status, protein,	There was a nonsignificant negative association between mean AF-alb and child growth indicators ($\beta = -0.07$; 95% CI: −0.27 to 0.13; $p = 0.257$), as well as with length velocity (β	5

	12 months follow-up		months, and 12 months from recruitment. At these respective sampling times, GM UFB1 pg/mL (detection %): 313.9 (98%), 167.3 (96%), and 569.5 (100%).				WAZ(14%), WLZ(2%): 12 months: LAZ(56%), WAZ(14%), WLZ(0.7%):	and energy intakes.	= –0.33; 95% CI:–0.70 to 0.05; $p = 0.084$). UFB1 concentrations were negatively associated with LAZ but not with other *Z*-scores at each sampling time.	
(Magoha et al. 2016)	Tanzania 143 infants less than 6 months of age. Three follow-ups (1st, 3rd and 5th months of age)	Longitudinal	Median values (% detectable) at 3 mo: 6 μg kg^{-1} (58%) AF, 124 μg kg^{-1} (31%) FUM. For infants, AF and FUM exposure ranges BW/day: 0.14 to 120 ng kg^{-1} and 0.005 to 0.88 g kg^{-1}, respectively.	AF FUM	HPLC	Maize flour	weight gain, length gain, age, WAZ (35%)/115 and LAZ (43%)/115	Feeding practices	Insignificant association was observed between exposure to FUM (OR = 0.23) or AF (OR = 0.97) and stunting or underweight.	5
(Chen et al. 2018)	Tanzania 114 children under 36 months of age	Longitudinal	With a detection rate of 72% and 80% had detectable levels of UFB1	AF FUM	UPLC-MS/MS	AFB1-lys (Urine)	At 24 months: HAZ (61%) WAZ (17%) WHZ (3%) At 36 months: HAZ (75%) WAZ (21%) WHZ: none	Dietary intake, socioeconomic status index.	No association was found between AF exposure and growth impairment as measured by stunting, underweight or wasting. However, FUM exposure was negatively associated with underweight.	6
(Gong et al. 2002)	Benin and Togo 480 children (aged 9 months to 5 years)	Cross-sectional	Detected in 99%. GM: 32.8 pg/mg.	AF	NR	AF-alb (Blood)	WAZ (29%), HAZ (33%), WHZ (6%)	Weaning status, agro-ecological zone, socioeconomic status, and age.	There was a strong association between increased AF-alb level and HAZ ($p = 0.001$) and WAZ ($p = 0.047$) but not with WHZ	5
(Sheila and Ohingo 2004)	Kenya 242 children (age 3-36 months)	Cross-sectional	Detected in 29% with range of 2–82 μg/kg.	AF	TLC	Weaning flour	Reported: HAZ (34%) WAZ (30%) WHZ (6%)	Weaning foods, education and income of the mother.	There was a significant association between wasted children and those who consumed AF-contaminated flour.	5
(Mahdavi et al. 2010)	Iran 182 lactating women with their exclusively breastfed infants aged 90–120 days	Cross-sectional	Detection in breast milk was 22 % and mean contamination: 6.96 ± 0.94 pg/ml.	AF	ELISA	AFM1 (Breast milk)	Reported in HAZ and WAZ	Exclusive breastfeeding, maternal energy intake, maternal height.	A significant association between the HAZ of infants and AFM1 was observed (β = -0.31 $p <$ 0.015). However, no significant correlation was found with WAZ.	6
(Shouman et al. 2012)	Egypt 46 children	Cross-sectional	Detection (median) ppm:	AF	TLC	AF-alb (Blood)	WAZ, HAZ, and Age.	Age, residence, maternal parity,	HAZ score showed a significant negative correlation with AFB1	4

(*continued*)

Table 1. Continued.

Author/year	Study setting/ study population	Study design	Detection rate (%)	Mycotoxin type	Technique	Matrix/type of food	Outcome measurement	Adjustment for covariates	Findings	Quality score
	(1 month to four and a half year)		36.96% (51.61) and 36.96% (50) for the children and their mother respectively.					education, and occupation.	level. AF-alb positive children had lower HAZ sores compared to AF-alb negative children ($r = -0.460$, $p = 0.001$).	
(Maleki et al. 2015)	Iran 85 children (aged 0.2 to 21 months)	Cross-sectional	Mean (range) ng/L: 5.91 ± 2.031 (2 to 10) with 100% detection.	AFM1	ELISA	AFM1 (Breast milk)	Measured age, birthweight	NR	No significant association was observed between AFM1 concentration and anthropometric data of infants.	4
(Kiarie 2016)	Kenya 204 children (aged 1–3 years)	Cross-sectional	98% food samples detected with an average of 21.3 ng/kg bw/day.	AF AFM1	ELISA	AFM1, maize and sorghum	Reported:HAZ (41%) WAZ (17%) WHZ (4%)	Age, dietary intake, breastfeeding, and location	AFM1 was negatively associated with HAZ ($\beta = -0.090$, $p = 0.047$). There was no association between total AF and HAZ, WAZ and WHZ.	6
(Ayelign et al. 2017)	Ethiopia 200 children (aged 1–4 years)	Cross-sectional	Detected in 17%	AF	LC-MS/MS	Urine	Reported: HAZ (45%) WAZ (17%) WHZ (1%)	Age, dietary intake and weaning status	There was no association between the different malnutrition categories (stunted, wasting and underweight) and AF exposure.	5
(McMillan et al. 2018)	Nigeria 58 children aged 6–48 months with severe acute malnutrition	Cross-sectional	Median (range) pg/mg albumin: 2.6 (0.2 to 59.2)	AF	LC-MS/MS	AFB1-lys with IDMS	Measured severe acute malnutrition (81%), MUAC, HAZ (74%) and WHZ	Age and type of residence	The association between stunting and AFB1-Lys was no significant after adjustment for malnutrition status (OR = quartile 3, 1.21; 95% CI: 0.086–31.45), and there was no correlation between AFB1-lys and WAZ. AFB1-lysine concentrations were significantly higher in stunted children compared to non-stunted, as well as in children with severe acute malnutrition compared to controls.	6
(Njumbe et al. 2013)	Cameroon 220 children (aged 1.5–4.5 years)	Cross-sectional	With a detection rate of 73%.	Multi-mycotoxins	LC-MS/MS	Urine	Reported: HAZ (39%) WAZ (37%) WHZ (23%)	Age, agro-ecological zones and weaning status	There was no association between the different malnutrition categories (stunted, wasting and underweight) and the mycotoxin concentrations detected in the urine significance differences were observed between the weaning categories and AFM1 concentration detected in the urine.	5

AF: aflatoxin; FUM: fumonisin; AFB1: aflatoxin B1; AFM1: aflatoxin M1; NR: not reported; ELISA: enzyme-linked immunosorbent assay; HPLC-MS: high-performance liquid chromatography-mass spectrometry; LC-MS/MS: liquid chromatography-mass spectrometry tandem mass spectrometry; UPLC-MS/MS: ultra performance liquid chromatography-tandem mass spectrometer; HPLC: high-performance liquid chromatography; TLC: thin layer chromatography; HAZ: height-for-age *Z*-score; WAZ: weight-for-age *Z*-score; WHZ: weight-for-height *Z*-score; LAZ: length-for-age *Z*-score; WLZ: weight-for-length *Z*-score; HAD: height-for-age difference; UFB1: urinary fumonisin B1; AF-alb: aflatoxin-albumin; AF-lys: aflatoxin-lysine; HIV: human immunodeficiency virus; GM: geometric mean; ppm: parts per million; MUAC: mid-upper arm circumference; IDMS: isotope dilution mass spectrometry; OR: odds ratio; CI: confidence interval; SD: units.

and head circumference however, were not reported consistently across the studies. Four cohort studies (Kimanya et al. 2010; Magoha et al. 2016; Natamba 2016; Leroy et al. 2018) and only one cross-sectional study (Shouman et al. 2012) did not report wasting data. Six cohort studies (Turner et al. 2007; Kimanya et al. 2010; Magoha et al. 2014, 2016; Natamba 2016; Leroy et al. 2018) and three cross-sectional studies (Mahdavi et al. 2010; Shouman et al. 2012; McMillan et al. 2018) did not report underweight data.

Dietary AF exposure and child growth

Two RCTs were retrieved (Hoffmann, Jones, and Leroy 2018; Kamala et al. 2018). A RCT in Tanzania indicated that AF intake was inversely associated with underweight (β = –0.007; 95%; CI: –0.009 to –0.0004; $P = 0.039$) (Kamala et al. 2018). In this study, the height-for-age *Z*-score (HAZ) and weight-for-height *Z*-score (WHZ) were not reported. Another RCT from Kenya showed that reducing dietary AF exposure had no effect on child length-for-age *Z*-score (LAZ) or on the prevalence of stunting at endline (Hoffmann, Jones, and Leroy 2018). A significant effect on child linear growth was found at midline: the intervention increased LAZ by 0.16 SD, and reduced the prevalence of stunting by seven percentage points. No significant effect was found on serum AFB1-lysine adduct levels at midline. This study only reported LAZ but not WAZ (weight for age *Z*-score) or WHZ.

Nineteen observational studies reported associations (both negative and positive) between AF exposure and malnutrition (as assessed by HAZ, WHZ, and WAZ) (Gong et al. 2002, 2004; Sheila and Ohingo 2004; Turner et al. 2007; Mahdavi et al. 2010; Shouman et al. 2012; Njumbe et al. 2013; Magoha et al. 2014, 2016; Maleki et al. 2015; Shirima et al. 2015; Natamba 2016; Kiarie 2016; Ayelign et al. 2017; Mitchell et al. 2017; Mahfuz 2017; Chen et al. 2018; McMillan et al. 2018; Leroy et al. 2018). Nine studies (Gong et al. 2002, 2004; Sheila and Ohingo 2004; Turner et al. 2007; Mahdavi et al. 2010; Shouman et al. 2012; Magoha et al. 2014; Natamba 2016; Leroy et al. 2018) reported dietary AF exposure was associated with at least one indicator of malnutrition that remained statistically significant after adjusting for confounders. Most of the studies were conducted in countries with a high prevalence of stunting.

Ten prospective cohort studies (Gong et al. 2004; Turner et al. 2007; Magoha et al. 2014, 2016; Shirima et al. 2015; Natamba 2016; Mahfuz 2017; Mitchell et al. 2017; Chen et al. 2018; Leroy et al. 2018) examined the association between dietary AF exposure and child malnutrition. Five of these studies (Gong et al. 2004; Turner et al. 2007; Magoha et al. 2014; Natamba 2016; Leroy et al. 2018) reported that the AF exposure was negatively correlated with HAZ. One study (Magoha et al. 2014) reported a small, but a significant inverse association between AFM1 exposure levels and WAZ. Another study from Uganda (Natamba 2016) reported AF exposure was associated with decreased infant linear growth in HIV-positive pregnant women. However, five of these cohort studies (Shirima et al. 2015; Magoha et al. 2016; Mahfuz 2017; Mitchell et al. 2017; Chen et al. 2018) reported that AF exposure was not significantly associated with indicators of child malnutrition. Despite the highest prevalence of stunting in a recent study from Tanzania (Chen et al. 2018), no association was found between AF exposure and growth impairment. Similar confounding factors have been used across each studies. Most of the cohort studies adjusted for potential confounding factors (Gong et al. 2004; Turner et al. 2007; Magoha et al. 2014, 2016; Shirima et al. 2015; Natamba 2016; Mahfuz 2017; Mitchell et al. 2017; Chen et al. 2018; Leroy et al. 2018). Five cohort studies (Turner et al. 2007; Magoha et al. 2014, 2016; Natamba 2016; Leroy et al. 2018) did not report associations with WHZ and three cohort studies (Magoha et al. 2016; Natamba 2016; Leroy et al. 2018) did not report WAZ. Only one study (Turner et al. 2007) showed a dose-dependent relationship between AF-alb, and WAZ and HAZ in children.

Two observational studies (Gong et al. 2004; Turner et al. 2007) reported that higher AF exposure was associated with a decrease in height. Additionally, increased levels of dietary AF exposure were strongly related to a lower level of weight-for-age in the infants.

Nine cross-sectional studies (Gong et al. 2002; Sheila and Ohingo 2004; Mahdavi et al. 2010; Shouman et al. 2012; Njumbe et al. 2013; Maleki et al. 2015; Kiarie 2016; Ayelign et al. 2017; McMillan et al. 2018) reported on AF exposure and child growth indicators. Of these studies, three studies (Gong et al. 2002; Mahdavi et al. 2010; Shouman et al. 2012) found AF level was related with decreased HAZ. A study conducted in Benin and Togo (Gong et al. 2002) reported AF exposure was positively related to underweight. A study from Kenya (Sheila and Ohingo 2004) showed that the consumption of AF-contaminated flour was related to wasting in children, but it was not related to the other anthropometric indices. Six studies (Sheila and Ohingo 2004; Njumbe et al. 2013; Maleki et al. 2015; Kiarie 2016; Ayelign et al. 2017; McMillan et al. 2018) reported that there was no association between AF and stunting. Only one study (Shouman et al. 2012) did not report associations with WAZ and three studies (Mahdavi et al. 2010; Shouman et al. 2012; McMillan et al. 2018) did not report them with WHZ. Two studies (Gong et al. 2002; Mahdavi et al. 2010) reported a dose-dependent decrease in WAZ and HAZ in AF exposed children.

AF exposure was related with a decreased in WAZ, HAZ and WHZ scores when using various biomarkers of exposure; six observational studies (Gong et al. 2002, 2004; Turner et al. 2007; Shouman et al. 2012; Natamba 2016; Leroy et al. 2018) reported AF exposure in blood, and two studies (Mahdavi et al. 2010; Magoha et al. 2014) in breast milk. There were variations in findings with various biomarkers of exposure.

Dietary FUM exposure and child growth

A cluster RCT evaluated the effect of post-harvest mitigation strategies in preventing and reducing AF and FUM contamination in maize and subsequent dietary exposure in

Tanzanian infants. FUM intake was inversely associated with underweight (β = –0.041; 95% CI: P = 0.067 to –0.014; $P = 0.003$) (Kamala et al. 2018).

Four prospective cohort studies reported FUM exposure and its association with child growth indicators (Kimanya et al. 2010; Shirima et al. 2015; Magoha et al. 2016; Chen et al. 2018). Two of these cohort studies, one using urinary FUM and the other food intake (Kimanya et al. 2010; Shirima et al. 2015) were associated with increased stunting in children. There was a mean difference of 1.8 cm reduced growth in children in the highest urinary FUM B1 (UFB1) quartile compared to the lowest in Tanzanian children (Shirima et al. 2015). These two studies (Kimanya et al. 2010; Shirima et al. 2015) demonstrated a non-significant dose-response relationship of FUM exposure and linear growth. Another cohort study (Magoha et al. 2016) reported an insignificant association between FUM exposure and stunting or underweight. A study from Tanzania (Chen et al. 2018) found that FUM exposure was associated with underweight but not with stunting.

Two observational studies (Kimanya et al. 2010; Magoha et al. 2016) have shown that FUM exposure negatively affects weight or length at 12 months and was associated with impaired growth.

Strength of evidence

Given the observational nature of most studies and inconsistent results, the overall quality of evidence was very low. In the summary of findings (Table 2), we differentiated the number of studies examining an association from the number of studies reporting a significant association. There were moderate to significant methodological limitations and serious inconsistency of results between studies. There was no serious indirectness of evidence. Table 3 shows the details of the evidence quality appraisal. The majority of the included studies used prospective cohort study designs. Some of these studies did not consistently account for potential covariates such as diet, seasonality and socioeconomic status. In addition, inconsistent sampling techniques and methods of mycotoxin analysis, i.e. detection of different subsets of related molecules, were reported in these studies and challenged comparisons of studies and findings.

Dietary mycotoxins exposure and birth outcomes

Description of included studies

Studies took place in Africa (50%), Asia (12.5%), and the Middle East (37.5%). The studies were published between 1989 and 2018. The studies were observational: cross-sectional studies ($n = 5$; 62.5%), and prospective cohort studies ($n = 3$; 37.5%). We were unable to find the full-text of one study (Andrews-Trevino 2017). Table 4 provides full study characteristics and scores on the Newcastle-Ottawa scale in Supplementary material Appendix S2). One cohort study received seven of the maximum nine score.

Of the five prospective cohort studies that assessed the relationship between maternal AF exposure and birth weight, four studies reported a negative correlation (Abdulrazzaq et al. 2002, 2004; Andrews-Trevino 2017; Lauer 2018), while a prospective cohort study from Gambia (Turner et al. 2007) showed that neither maternal nor cord blood AF-albumin was significantly associated with lower birth weight. Three cross-sectional studies (Vries 2008; Sadeghi et al. 2009; Shuaib et al. 2010) showed that detection of AF in maternal or cord blood was associated with lower birth weight. One cross-sectional study (Maxwell et al. 1994) showed no association between in utero AF exposure in cord blood samples and infant birth weight. In Kenya (Vries 2008), the mean birthweight of female babies of AF-positive mothers was 255 g less than the mean birthweight of females born to AF-negative mothers.

One population-based case–control study conducted in a Texas Mexican-American population (Missmer et al. 2006) reported that FUM exposure during early-gestation increased the risk of neural tube defects.

Strength of evidence

The overall quality of evidence was graded as being very low due to concerns regarding methodological limitations. Studies on dietary mycotoxins exposure and low birth weight had small sample sizes, and thus may not be sufficiently powered to detect important population effects. Furthermore, most of the studies did not adjust for other factors that could affect low birth weight.

Dietary AF exposure and immune system

No study reported immunity suppression in children under five years of age. One study in South Africa (Wood 2016) reported that ochratoxin (OTA) plasma levels correlated with the expression of activation markers (cytokines).

Insufficient data were available to grade evidence with regard to dietary AF exposure and potential associations with immune system in the children.

Dietary mycotoxin exposure and morbidity

Description of included studies

Studies took place in Africa (85%), Asia (10%), and North America (1%). The studies were published between 1982 and 2016, with 15 (75%) studies published before 2000. The studies were observational: cross-sectional studies ($n = 9$; 45%), case–control studies ($n = 10$; 50%) and prospective cohort studies ($n = 1$; 5%). We were unable to find the full-text of one study (Quiepo 1990) and only the abstract was included in the present review. Table 5 provides full study characteristics and scores on the NOS in Supplementary material Appendix S2. In the case of case–control studies, some of the controls selected from the general population are not likely to be representative of those at risk of becoming cases.

Table 2. Summary of findings.

Exposure type	Summary of review findings with their contributing studies	Confidence in the evidence	Explanation of confidence in the evidence assessment
Aflatoxins exposure and health outcomes			
Stunting	Several observational studies have shown a potential association/ correlation between AF exposure and childhood stunting. Eight studies found a negative association between increased AF level and stunting (Gong et al. 2002, 2004; Turner et al. 2007; Mahdavi et al. 2010; Shouman et al. 2012; Magoha et al. 2014; Natamba 2016; Leroy et al. 2018), while twelve studies reported that there was no association between AF and stunting (Sheila and Ohingo 2004; Njumbe et al. 2013; Shirima et al. 2015; Maleki et al. 2015; Kiarie 2016; Magoha et al. 2016; Ayelign et al. 2017; Mahfuz 2017; Mitchell et al. 2017; Chen et al. 2018; Hoffmann, Jones, and Leroy 2018; McMillan et al. 2018).	Very low	This finding was graded as very low confidence because of moderate to significant methodological limitations coupled with the serious inconsistency of results between studies. No serious indirectness.
Wasting	10 studies reported on the association between AF levels and wasting (Gong et al. 2002, 2004; Njumbe et al. 2013; Maleki et al. 2015; Shirima et al. 2015; Kiarie 2016; Ayelign et al. 2017; Mahfuz 2017; Mitchell et al. 2017; Chen et al. 2018). Only one study (Sheila and Ohingo 2004) showed consumption of AF-contaminated flour was related to wasting in children, but it was not related to the other anthropometric indices.	Very low	This finding was graded as very low confidence because of moderate to significant methodological limitations and concerns regarding inconsistencies and imprecision. There was no serious indirectness.
Underweight	Sixteen studies reported on the association between AF levels and underweight (Gong et al. 2002, 2004; Sheila and Ohingo 2004; Turner et al. 2007; Mahdavi et al. 2010; Njumbe et al. 2013; Magoha et al. 2014, 2016; Shirima et al. 2015; Maleki et al. 2015; Kiarie 2016; Ayelign et al. 2017; Mitchell et al. 2017; Mahfuz 2017; Chen et al. 2018; McMillan et al. 2018). Only one study (Kamala et al. 2018) reported a significant inverse association between AF exposure and weight for age *Z*-score.	Very low	This finding was graded as very low confidence because of moderate to significant methodological limitations and concerns regarding inconsistencies and imprecision. There was no serious indirectness.
Morbidity	The limited studies addressed varied types of morbidities (neonatal jaundice, acute lower respiratory infections, Plasmodium falciparum parasitemia, hepatitis B), which are not consistently similar morbidities in the studies.(Allen et al. 1992; Denning et al. 1995; Sodeinde et al. 1995; Turner et al. 2000)	Very low	Serious methodological limitations with serious inconsistencies and substantial concerns regarding the adequacy of data. There was a serious imprecision.
Kwashiorkor or marasmus	Most of the studies also consistently reported statistically significant association (Hendrickse et al. 1982; Coulter et al. 1986; Ramjee et al. 1992; Hatem et al. 2005; Tchana, Moundipa and Tchouanguep 2010) or difference in percentage in the level of AF between children with kwashiorkor and control groups (Coulter et al. 1986; De Vries, Lamplugh, and Hendrickse 1987; Household and Hundt 1991; Oyelami et al. 1995; Oyelami et al. 1997, 1998).	Very low	Overall the studies considered fair sample sizes with better exposure measuring equipment or method. On top of that, we are suspecting less publication bias. On the other hand, the studies showed variation in measuring the direct relation of AF and kwashiorkor or marasmus. Additionally, the studies have sensible methodological limitation.
Birth outcome	Six studies assessed the relationship between maternal or infant AF exposure and birth weight. Five studies (De Vries and Maxwell 1989; Abdulrazzaq et al. 2002, 2004; Shuaib et al. 2010; Andrews-Trevino 2017) reported a negative correlation while a study from Nigeria (Maxwell et al. 1994) showed that detection of AF in cord blood was not correlated with birth weight.	Very low	Substantial concerns regarding the adequacy of data and serious methodological limitations. There was some inconsistency of results between studies.
Fumonisins exposure and health outcomes			
Stunting	Two studies (Kimanya et al. 2010; Shirima et al. 2015) reported FUM were negatively associated with Stunting but not with the other *Z*-scores, one from urinary FUM and the other from food contamination. These two studies demonstrated that dose-effect relationships have been established in studies using FUM exposure and growth in length, although not significant. Another study (Magoha et al. 2016) reported insignificant association between exposure to FUM and stunting.	Very low	Though all the studies targeted less than 5 years old children still there is variation in the age groups included. Though all are cohort studies in Tanzania, the follow-up period and the season varies. No serious methodological limitation, indirectness, inconsistency with undetected publication bias.
Wasting	Of the two studies that reported on the association between FUM and wasting, no association has been reported (Shirima et al. 2015; Chen et al. 2018).	Very low	Some methodological limitations and imprecision. The extent of coherence unclear due to limited data, but findings were similar across the studies.
Underweight	Of the three studies that reported on the association between FUM and underweight, one study (Magoha et al. 2016) reported insignificant association between exposure to FUM and underweight. Another two studies from Tanzania (Chen et al. 2018; Kamala et al. 2018) found FUM exposure was negatively associated with underweight.	Very low	No serious methodological limitation, indirectness, inconsistency with undetected publication bias. However, there is limited evidence from published studies.
Birth outcome	Showed a significant association between FUM exposure during pregnancy with having neural tube defects (NTD) in newborns (Missmer et al. 2006).	Very low	The study is methodologically better but with some problem in precision and directness. The extent of consistency is unclear due to limited evidence from published studies.

Table 3. Quality of evidence of the association between mycotoxins exposure and child growth failure, morbidity and immunity.

No. studies (design)	Methodological limitations	Inconsistency	Indirectness	Imprecision	Publication bias	Quality of the evidence
Aflatoxins exposure and child growth failure, morbidity and immunity						
Stunting 19 Observational)	Serious limitations	Serious inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Wasting (11 observational)	Serious limitations	Some inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Underweight (16 observational)	Serious limitations	Some inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Birth outcomes	Serious limitations	Some inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Kwashiorkor or Marasmus (12 Observational)	At serious borderline	Not serious	No serious indirectness	Not serious	Undetected	⊕◯◯◯ Very low
Morbidity (4 Observational)	Serious limitations	Some inconsistencies	No serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ Very low
Fumonisins exposure and child growth failure, morbidity and immunity						
Stunting (4 observational)	Some limitations	Some inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Wasting (2 observational)	Some limitations	No inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Underweight (2 observational)	Some limitations	Some inconsistencies	No serious indirectness	Some imprecision	Undetected	⊕◯◯◯ Very low
Birth outcomes (1 Observational)	Some limitations	No other studies to compare the level of inconsistency	Serious indirectness	Serious imprecision	Undetected	⊕◯◯◯ Very low

Dietary mycotoxin exposure and kwashiorkor or marasmus

Associations with kwashiorkor or marasmus have only been reported for AF. Four hospital-based case–control studies (Coulter et al. 1986; De Vries, Lamplugh, and Hendrickse 1987; Ramjee et al. 1992; Hatem et al. 2005) reported that AF was found more frequently in the serum and urine of children with kwashiorkor, than in normal and marasmic controls. Conversely, in a study from Kenya (De Vries, Lamplugh, and Hendrickse 1987) and South Africa (Ramjee et al. 1992), children with kwashiorkor had lower urinary concentrations of AF. Two studies (Coulter et al. 1986; Hatem et al. 2005) reported there was no AF detected in the age-matched controls that were healthy individuals or with a minor illness. No study was conducted in a community setting.

Two case–control studies (Hendrickse et al. 1982; Tchana, Moundipa, and Tchouanguep 2010) reported that AF were detected at higher concentrations in children with kwashiorkor or marasmic-kwashiorkor than those in the control or marasmus group. However, in South Africa (Househam and Hundt 1991), no AF were reported in either the control or the urine of children hospitalized with kwashiorkor or marasmus. Both studies used different control groups.

In the Philippines (Quiepo 1990), a significant inverse correlation was found between AF exposure and mortality in children with acute respiratory infections, but another study (Denning et al. 1995) from the same country did not confirm this finding.

A case–control study in Nigeria (Sodeinde et al. 1995) showed that the presence of any serum AF were risk factors in neonatal jaundice. However, another study (Ahmed et al. 1995) conducted in the same country showed that there was no correlation between the severity of hyperbilirubinemia and serum AF levels.

A study in South Africa (Adhikari, Ramjee, and Berjak 1994) reported in children with AF-positive serum, significantly lower hemoglobin levels, a longer duration of edema, an increased number of infections, and a longer duration of hospital stay compared with the AF-negative group of kwashiorkor children. Two cross-sectional studies from Gambia (Allen et al. 1992; Turner et al. 2000) revealed that hepatitis B virus-positive carriers have higher levels of AF adducts than those with a negative status.

None of the above-reported studies was longitudinal. Most of the studies are case–control studies and there were limitations in matching the cases with the controls in terms of sex, age and health status of the children. Some of the studies used children with kwashiorkor as cases and marasmus as controls, while others used children with kwashiorkor and marasmus as cases and other healthy individuals as controls. Sample sizes varied from 40 to 548 in the case–control and from 37 to 444 in the cross-sectional studies. For the studies of AF exposure and children with kwashiorkor or marasmus, residual bias was not well-controlled in the analyses.

Strength of evidence

Overall, the certainty for the association between dietary mycotoxin exposure and morbidity was very low, mainly because of methodological limitations and inconsistencies. There was a serious level of imprecision (Table 3). The limited studies addressed varied types of morbidities (neonatal jaundice, acute lower respiratory infections, *Plasmodium falciparum* parasitemia, hepatitis B), which are not consistently similar morbidities in the studies. There was considerable incompleteness of reporting and lack of information. Excluding studies with low quality assessment would not alter the outcome of the present review as the overall quality of evidence is very low.

Table 4. Summary of studies on the association between aflatoxins exposure and birth outcomes.

Author/year	Study setting/ study population	Study design	Detection rate (%)	Mycotoxin type	Technique	Matrix	Outcome measurement	Adjustment for covariates	Findings	Quality score
(Lauer 2018)	Uganda 220 mother-infant pairs.	Prospective cohort	100% samples detected ranging from 0.71–95.6 pg/mg albumin.	AF	HPLC	Maternal serum	Birth weight, WAZ, LAZ, WLZ, and HCZ	Education, gestational age at birth.	Elevations in maternal AFB-Lys levels were significantly associated with lower weight (β: 0.07; 95% CI: 0.13 to −0.003; $p = 0.040$) and smaller head circumference ($\beta = -0.26$; 95% CI: −0.49, −0.02; $p = 0.035$).	7
(Shuaib et al. 2010)	Ghana 785 pregnant women attending antenatal care	Cross-sectional	With average (range) pg/mg: 10.9 ± 19.00 (0.44–268.73).	AF	HPLC	AFB1-lys	Measured birthweight	Malaria parasitemia, anemia and worm infections.	AF levels in the highest quartile were significantly associated with LBW (OR, 2.00; 95% CI, 1.22–3.28). There was a trend of increasing risk for LBW compared to participants in the lowest quartile.	6
(Abdulrazzaq et al. 2002)	United Arab Emirates 201 women	Prospective cohort	With 54.7% detection rate.	AF	HPLC	Umbilical cord blood	Baby's weight	gestational ages	There was a significant negative correlation ($r = -0.63$, $p < 0.001$) between birthweight and levels of AF.	5
(Abdulrazzaq et al. 2004)	United Arab Emirates 250 women admitted to hospitals	Cross-sectional	With detection rate in 67% cord and 68% in maternal samples.	AFM1	HPLC	cord blood and Maternal samples	Baby's weight	NR	Strong negative correlation between AFM1 levels in cord blood and birth weight ($r = -0.565$, $p = 0.001$) and between maternal serum AFM1 concentration and birthweight ($r = -0.654$, $p = 0.0001$). No association b/n AFM1 in maternal or cord blood and rates of jaundice or infection.	4
(Sadeghi et al. 2009)	Iran 160 women	Cross-sectional	Detection in 98.1% with average concentration (Range) ng/kg: 8.2±5.1 (0.3-26.7)	AFM1	ELISA	Breast milk	Height and weight at birth	NR	Significant association between AFM1 concentration and height at birth ($p < 0.01$).	4
(Vries 2008)	Kenya 125 primigravidae	Cross-sectional	With a detection rate of 53%	AF	HPLC	Cord Blood	Baby's weight	seasonal variation	The mean birth weights of females born to AF-positive mothers were significantly lower (255 g) than those born to AF free mothers. No association between AF in maternal and cord blood.	5
(Maxwell et al. 1994)	Nigeria 625 babies	Cross-sectional	Detection rate was 14.6%	AF	HPLC	Blood	Baby's weight	NR	Detection of AF in cord blood showed no correlation with birthweight.	4
(Andrews-Trevino 2017)	Nepal 1484 infants	Prospective cohort	Maternal serum 3.4(±8.4) pg/mg of LBW	AF	NR	Maternal serum	LBW (20%)	Maternal schooling, dietary diversity, maternal stature,	Significant association between maternal AF exposure and LBW.	NA

AF: aflatoxin; AFB1: aflatoxin B1; AFM1: aflatoxin M1; NR: not reported; ELISA: enzyme-linked immunosorbent Assay; HPLC: high-performance liquid chromatography; LAZ: length-for-age *Z*-score; WAZ: weight-for-age *Z*-score; WLZ: weight-for-length *Z*-score; HCZ: head circumference *Z*-score; AFB1-Lys: aflatoxin B (1)-lysine adduct; MUAC: mid-upper arm circumference; NA; not applicable as only an abstract was found.

Table 5. Summary of studies on the associations between mycotoxins exposure and morbidity.

Author/year	Study area/population	Study design	Technique	Mycotoxin type	Matrix	Detection rate (%)	Findings	Quality score
(Wood 2016)	South Africa 151 HIV exposed, uninfected infants	Prospective cohort	ELISA	OTA	Blood	NR	OTA plasma levels correlated with expression of activation markers.	5
(Coulter et al. 1986)	Sudan 584 children	Case–control	HPLC	AF	AF-alb and urine	Sera of 11.6% kwashiorkor, 6.1% marasmic-kwashiorkor, but in none of the controls and only once in marasmus.	The difference between the detection rate in kwashiorkor and controls was significant ($p < 0.05$).	5
(De Vries, Lamplugh, and Hendrickse 1987)	Kenya under 5 years of age Cases: 31 (Marasmus, Marasmus-kwashiorkor, Kwashiorkor) and Control: 10	Case–control	HPLC	AF	Blood urine	Serum: kwashiorkor (64%), marasmic-kwashiorkor (50%), marasmus (36%) control:30% Urine: kwashiorkor (42%), marasmic-kwashiorkor (60%), marasmus (45%) control:75%	AF were detected most frequently and at highest concentrations in the sera of kwashiorkor who, conversely, showed AF least frequently in the urine.	5
(Househam and Hundt 1991)	South Africa 320 children, aged 1-5 years	Case–control	HPLC	AF	Urine	AFs were not detected in these samples	No AF exposure occurred in either the community group or the children hospitalized with kwashiorkor or marasmus.	7
(Ramjee et al. 1992)	South Africa 109 children, aged 6 months to 2 years	Case–control	TLC & HPLC	AF	AF-alb and urine	Serum/109: 49% control, 31% marasmus, 56% underweight, 56% kwashiorkor Urine/50: 25% control, 10% marasmus, 16% kwashiorkor	The serum/urine ratio was significantly higher in the kwashiorkor group than in the other groups. The control group, however, had a higher proportion of urine AFs than the kwashiorkor group.	6
(Sodeinde et al. 1995)	Nigeria 387 children, 327 jaundiced neonates and 60 nonjaundiced controls	Case–control	HPLC	AF	Blood	27.4% Jaundice 16.6% Control	The presence of any serum AF are risk factors in neonatal jaundice with adjusted OR of 2.68 (95% CI: 1.18-6.10); these are statistically significant.	7
(Ahmed et al. 1995)	Nigeria 64 Jaundice, 60 non-jaundice	Case–control	HPLC	AF	Blood	Case-28% control-20%	There was no correlation between the severity of hyperbilirubinemia and serum AF levels. Comparison of mean birthweights between the groups showed no significant differences.	5
(Hendrickse et al. 1982)	Sudan 250 children in urine, 177 in the serum of the same population	Case–control	HPLC and TLC	AF	AF in serum and urine	Serum: 36.4% kwashiorkor, 21.9% marasmic-kwashiorkor, 19.3% marasmus and 15.9% in the controls. Urine: 33.3% kwashiorkor, 25% marasmic-kwashiorkor, 25.7% marasmus and 19.8% in the controls.	AFs were detected at higher concentrations in sera from children with kwashiorkor than in the other malnourished and control groups. The difference between children with kwashiorkor or marasmic-kwashiorkor and those in the control or marasmus groups was significant.	5
(Hatem et al. 2005)	Egypt 70 infants	Case–control	TLC	AF	AF in serum and urine	80% kwashiorkor, 46.7% marasmus and none in the controls.	The mean serum and urinary concentrations of AF were significantly higher in infants with kwashiorkor than marasmus. There	4

							was no AF detected in the control group.	
(Missmer et al. 2006)	Mexican-American 409 women (184 cases and 225 control)	Case–control	sa:so ratio in serum using HPLC with FD	FUM	Maternal serum	NR	FUM exposure during the first trimester was associated with increased odds ratios of having an NTD affected pregnancy.	7
(Tchana, Moundipa and Tchouanguep 2010)	Cameroon 76 children (aged 13 months to 12 years)	Case–control	HPLC	AF	Urine	Kwashiorkor = 35.5% Marasmic-kwashiorkor = 45.5% Controls = 11%	There was a statistically significant difference in AFB1 between children suffering kwashiorkor or marasmic kwashiorkor, and healthy children in the control.	6
(Coulter et al. 1986)	Sudanese children, 27 with (16 kwashiorkor, 1 marasmic-kwashiorkor, 10 marasmus) and 13 with liver disease, aged 11-36 months	Cross-sectional	HPLC and TLC	AF	Liver Biopsies	Serum: kwashiorkor = 37.5%, Urine: 26.7% kwashiorkor, 44.4% marasmus, Liver: 31.2% kwashiorkor but not in the others.	AFs were detected in the livers of children with kwashiorkor but not in marasmus.	3
(Adhikari, Ramjee, and Berjak 1994)	South Africa 36 kwashiorkor children, aged 6 months to 2 years	Cross-sectional	TLC and HPLC-FD	AF	Blood	58%	Compared with the AF-negative group, the children scored as AF-positive showed a significantly lower hemoglobin level ($p = 0.02$), a longer duration of edema ($p = 0.057$), an increased number of infections ($p = 0.037$), and a longer duration of hospital stay ($p = 0.008$).	4
(Oyelami et al. 1995)	Nigeria 37 children died from kwashiorkor 18 and other diseases 19, aged 7-84 months	Cross-sectional	HPLC	AF	Autopsy brain	81%	A more frequent detection of AFB1 and its reversible metabolite aflatoxicol, in the brain of patients who died with kwashiorkor compared with the other group.	3
(Oyelami et al. 1997)	Nigeria 40 children died from Kwashiorkor 20 versus miscellaneous disease 20, aged 4-72 months	Cross-sectional	HPLC	AF	Autopsy lung	78%	AFs were detected in 18 children who died of kwashiorkor and in 13 of those who died from miscellaneous diseases. No significant difference in the detection rate between the two groups.	3
(Oyelami et al. 1998)	Nigeria 45 children died from kwashiorkor 24 versus miscellaneous disease 21	Cross-sectional	HPLC	AF	Autopsy kidney	60%	AFs were detected in 18 children who died of kwashiorkor and in 13 of those who died from miscellaneous diseases. No difference was found between the frequency of detection, type of AF detected, or mean concentrations of total AFs in the kidney specimens of the kwashiorkor children when compared to the kidney specimens of children who died from miscellaneous diseases.	3
(Denning et al. 1995)	Philippines 115 children, mean age 2.1 years	Cross-sectional	ELISA	AF	Blood Urine	Serum = 33% 64/65 in urine	There was no relationship between the concentration of urinary AF metabolites and acute lower respiratory infection.	3

(*continued*)

Table 5. Continued.

Author/year	Study area/population	Study design	Technique	Mycotoxin type	Matrix	Detection rate (%)	Findings	Quality score
(Allen et al. 1992)	Gambia 323 children aged 3-8 years	Cross-sectional	HPLC	AF	Blood	Nearly all	AF-alb adduct levels were higher in children who were HBsAg positive and in children with Plasmodium falciparum parasitemia than in controls.	5
(Turner et al. 2000)	Gambia 444 children aged 3–4 years	Cross-sectional	ELISA	AF	Blood	100%	When acutely infected and chronic carriers were combined, there was a significant ($p < 0.03$) increase in AF-alb levels compared to non-infected children.	5
(Quiepo 1990)	Philippines 114 children	Cross-sectional	ELISA	AF	Blood	66.7%	A significance inverse correlation was found between AF exposure and mortality in children with acute respiratory infections.	NA

NR: not reported; OTA: ochratoxin; AF: aflatoxin; FUM: fumonisin; ELISA: enzyme-linked immunosorbent assay; HPLC: high-performance liquid chromatography; HPLC-FD: high-performance liquid chromatography with fluorescence detection; NA; not applicable as only an abstract was found. TLC: thin layer chromatography; NTD: neural tube defect; OR: odds ratio; HIV: human immunodeficiency virus; AF-alb: aflatoxin albumin adduct; AFB1: aflatoxin B1; sa/so: sphinganine/sphingosine HBsAg: HBV surface antigen.

Discussion

Summary of the main findings

To the best of our knowledge, the present review is the first systematic effort to investigate the potential association between dietary mycotoxin exposure and child growth, immune system, morbidity, and mortality. The overall quality of the evidence was quite low and adds to uncertainty around the association of dietary mycotoxins with child malnutrition. Despite the increasing evidence for a potential association between FUM exposure and child growth, further research is needed on this relationship and the mechanisms by which FUM may cause growth impairment. Similarly, the association between AF exposure and immunity and birth outcomes remains unclear. Similar findings have been observed between AF exposure and children with kwashiorkor or marasmus, though residual bias was not well controlled in the analyses. Overall, the certainty of the estimates for the association between dietary mycotoxin exposure and child growth failure and malnutrition was very low, mainly because of risk of bias and inconsistency (Table 3). These results suggest that further research is likely to have an important effect on our confidence in the estimation of association and could change the estimate.

Based on the available evidence from two cluster RCTs and twenty observational studies, we have examined the association of dietary mycotoxin exposure on child malnutrition. There were no individual randomized controlled trials. We found inconsistent results in the association between mycotoxins exposure and child growth indicators. This inconclusive evidence might be due to considerable heterogeneity among studies in terms of matrices, variation in measurement methods, exposure period, seasonal variation, failing to adjust to confounders, differences in study populations and limited sample size. Various studies used different body fluids (such as urine, breast milk, and blood-plasma/serum) and food samples to measure AF and AF-metabolites such as AFM1, and biomarkers of exposure and effect, and their association with child growth. The co-existence of both positive and null results is not necessarily an indication of inconsistency. We did not find a plausible explanation for the variability of results and we fail to attribute it to differences in the use of different biomarkers and analytical methods. Therefore, the comparability of these studies is not warranted.

Although the mechanisms by which AF causes growth impairment in humans is not clear yet, various biologically plausible pathways have been identified. These include zinc deficiency, inhibition of protein synthesis leading to impaired metabolism and enterocyte damage ultimately leading to systemic immune activation (Smith, Stoltzfus, and Prendergast 2012).

To date, the mechanistic pathway how FUM exposure leads to growth impairment is not well known. However, FUM-induced inhibition of ceramide synthase affects sphingolipid metabolism, which compromises the cellular wall, and may also lead to increased direct intestinal

permeability or by inhibiting the regeneration of the epithelial barrier (Smith, Stoltzfus, and Prendergast 2012).

The timing of exposure is critical at early stages of life and delayed adverse effects require integration of chronic intake estimates (Paustenbach 2001). The introduction of complementary foods and family foods marks a significant increase in AF exposure, as demonstrated by studies in the Gambia, Benin, and Tanzania (Gong et al. 2003; Turner et al. 2007; Shirima et al. 2013). Therefore, one of the approaches to reduce AF contamination in complementary foods is implementing AF prevention measures, particularly post-harvesting practices.

Given that AF in urine represent exposure over the previous 24–48 hours (Wild 1992), this measurement could only be useful to assess indices that are sensitive to acute changes to nutritional status. Thus, AFM1 levels in urine are used as a short-term biomarker of AFB1 exposure (Gan et al. 1988). As the AF-albumin adduct provides a measure of chronic exposure (two to three months) (Wild 2002), this measurement is useful to assess chronic nutritional statuses such as stunting or LAZ. In chronically-exposed individuals, the urinary concentration of AFB1-N7-guanine in two separate studies and urinary AFM1 strongly correlated with AF intake (Zhu et al. 1987; Groopman et al. 1992, 1993). Furthermore, the concentration of AF-albumin in serum was strongly correlated with AF intake (Gan et al. 1988; Wild 1992). However, when there is extensive metabolism of the parent toxin to various metabolites or unmetabolised AFB1 occurs in the urine of exposed individuals, no significant correlation with intake is obtained (Groopman et al. 1993). As a result, various studies indicated that urinary AFB1 is not a useful indicator of AF exposure (Groopman et al. 1992, 1993; Wild 2002). Most of the AF exposure in urine were reported in AFB1, but urinary AF-N7-guanine would be regarded as high levels of AF exposure (Egner et al. 2006). However, studies do not appear to differ when exposure measured in AFB1-lys in blood and AFM1 in breast milk. To date, robust biomarkers of exposure and effect in biological matrices are not available.

The association between AF biomarkers and growth might be confounded by many factors. Various studies did not take into account environmental exposures, household socioeconomic status, maternal health in pregnancy, and inadequate nutrition and hygiene practices that contribute to intergenerational cycles of poor health and converge with poverty to increase risks of stunting (Black et al. 2008).

This inconclusive evidence might arise also from using multiple measuring techniques to detect AF across various studies. The variation in measurement methods leads to having different detection limits, but the results from HPLC (high-performance liquid chromatography) and ELISA (enzyme-linked immunosorbent assay) are generally comparable (McCoy et al. 2008). AFM1 may form low levels of albumin adducts detectable by ELISA with a possible drawback of cross-reactivity. Quantitative determination of metabolites using LC-MS/MS (liquid chromatography-mass spectrometry and tandem mass spectrometry) shows high specificity and sensitivity (McCoy et al. 2005).

We were not able to establish seasonal patterns of exposure with child growth failures as there was a dearth of available information with regard to harvesting time and storage activities.

Maternal AF exposure during pregnancy was linked with weight and length at birth (Maxwell et al. 1994; Abdulrazzaq et al. 2002, 2004; Vries 2008; Sadeghi et al. 2009; Shuaib et al. 2010; Andrews-Trevino 2017). This might be due to the inhibition of protein synthesis, caused by AF-induced disruption to RNA synthesis (Yu et al. 1988). This can result in physical alterations to the intestine, leading to malabsorption of nutrients and impaired intestinal barrier function, similar to the pathology in environmental enteropathy (Smith, Stoltzfus and Prendergast 2012). Chronic AF exposure could contribute to anemia through different mechanisms related to immune activation and enteropathy: a decreased capacity of the intestine to absorb essential nutrients such as iron; a decrease in erythropoiesis arising from chronic inflammation; and reduced availability of iron due to hepcidin upregulation (Smith et al. 2017). Alternatively, maternal characteristics that influence birth weight were not investigated in these studies. Zinc deficiency, pre-pregnancy weight or maternal body mass index, maternal height, are all indicators of maternal nutritional status. Environmental and socioeconomic factors also influence birth weight, as well as illnesses encountered in pregnancy such as infections, hypertensive disorders, and diabetes mellitus. Anemia during pregnancy is particularly a serious health issue and can consequently lead to LBW.

Therefore, this merits further research with rigorous study designs and adequate cohorts with large sample sizes to investigate the association of (multiple) mycotoxins on birth outcomes.

Studies which describe how FUM cross the human placenta are presently non-existent and evidence is only available for mice. It is unlikely however, that FUM is detectable in umbilical cord blood as the results in animals showed that very small amounts of FUM were detected in blood after exposure to relatively high levels of FUM (Riley and Voss 2006; JECFA 2011).

Evidence on AF in relation to the immune system in children is limited to an assessment of immunoglobulin A (IgA) in saliva (Turner et al. 2003) and T-cell activation markers (Wood 2016). Hence, a strong association cannot be established between mycotoxin/AF exposure and immune suppression of children to date.

A wide range of studies conducted in different countries of Africa suggested the potential association between AF exposure with kwashiorkor or marasmus. In the absence of a clinical pathway however, it remains unclear which role AF plays in the pathogenesis of kwashiorkor in children from the existing current studies.

Strengths and limitations of the systematic review

Our analyses were limited by the quality and reporting inconsistencies. The included studies were potentially underpowered, and did not enable further stratification by age,

complementary feeding status, exposure, and outcome definitions. Potential covariates were not assessed consistently.

This review focused on the dietary exposure to mycotoxins. Data on other exposure media, e.g. through dust and indoor environments by inhalation are scarce to non-existent. Despite a few studies on health outcomes due to mycotoxin exposure in dust and indoor environment however, there is no compelling evidence that exposure is likely to result in measurable health effects (Robbins et al. 2000; Dorribo et al. 2015).

We searched for all mycotoxins but we only found papers focusing on two mycotoxins, i.e. AF and FUM. However, studies have reported the co-occurrence of mycotoxins such as AF, FUM, deoxynivalenol, ochratoxin A, zearalenone, and trichothecenes (Smith et al. 2016). It is worth mentioning that most efforts are dedicated to AF and FUM without considering the whole spectrum of human mycotoxins exposure. The present review shows an overall dearth of information on this multi-contamination and associated health risks.

Implications for future research

In summary, evidence about the association between AF and FUM with growth impairment is inconclusive. Inconsistent study findings were observed, together with potential for residual bias and unaccounted confounding factors. We hence cannot rule out a possible association between dietary mycotoxins, in particular AF and FUM and child malnutrition. Future research is needed to investigate the threshold of chronic exposure to AF/FUM leading to child growth failure. Furthermore, robust experimental and longitudinal research with adequate sample size, and use of validated biomarkers of exposure and effect are required to ascertain the association of dietary mycotoxins exposure on child growth and immunity.

The potential synergistic effects of mycotoxins have been poorly considered to date. A study from Tanzania (Kimanya et al. 2014) highlighted the presence of co-exposures to multiple mycotoxins in children and suggested the potential for synergic effects. Further research on co-occurrence of mycotoxins and potential synergistic effects of the combined exposure is a new avenue for investigation.

Failure to control mycotoxins in areas where food is highly contaminated with multiple mycotoxins may lead to adverse health effects and economic losses due to lower resistance to diseases, counteraction of vaccine-induced immunity, and adverse effects on growth and reproduction (Desjardins et al. 2003). AFB1 has been reported to be synergistically interacting with Hepatitis B virus infection and was classified by the International Agency for Research on Cancer as a human carcinogen (IARC and International Agency for Research on Cancer 1993).

Despite the low quality and inconclusive evidence regarding mycotoxins and child malnutrition reported here, mitigation efforts to reduce mycotoxin contamination are needed for importance of other health outcomes, food security and economic benefits (Smith, Stoltzfus, and Prendergast 2012). Innovative approaches are urgently required to minimize mycotoxin-contaminated foods, especially in developing countries.

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