APPENDICES

Denno, DM, VanBuskirk, KM, Nelson, ZC, Musser, CA, Tarr, PI. (2016). Environmental enteric dysfunction: Advancing current knowledge. St. Louis, MO: Washington University Libraries. http://dx.doi.org/10.7936/K7WQ0228

APPENDICES

Appendix 1. Search terms for EED articles of interest.

Search terms for EED alone are in gray, malnutrition outcomes are in pink. A combined strategy, denoted in yellow was utilized for searches in the smaller WHO databases.

PubMed TE/ED completed April 1, 2010 (24156 Citations)
Step 1 (24875 Citations) ("Viruses" [Mesh] OR "Bacteria" [Mesh] OR "Parasites" [Mesh]) AND "Intestinal Diseases" [Mesh] Step 2 (2789652 Citations) ("malnutrition" OR "undernutrition" OR "micronutrient" OR "nutritional deficiency" OR "Nutrition Disorders" [Mesh] OR "child development" [Mesh] OR environmental OR recurrent OR recurring OR persistent OR chronic OR "Communicable Disease Control" [Mesh] OR handwashing OR "hand washing" OR toilet* OR sanitation OR hygiene OR drinking) Step 3 (478234 Citations) (enteropathy OR enteropathies OR diarrhea OR diarrhoea OR diarrhoeal OR diarrheal OR "Malabsorption Syndromes" [Mesh]) Step 2 AND 3 combined (93491 Citations) Step 4 (759 Citations) ("Diarrhea" [Mesh] AND "chronic disease" [Mesh]) 1, 378 Step 5 ("environmental enteropathies" OR "environmental enteropathy" OR "tropical enteropathy" OR "tropical enteropathies" OR "sprue, tropical " [MeSH] OR "tropical sprue" OR " Idiopathic Tropical Malabsorption Syndromes" OR " Idiopathic Tropical Malabsorption Syndrome") Step 6 (37074 Citations) "Intestinal Absorption" [Mesh]

Step 1 OR (Step 2 AND 3) OR Step 4 OR Step 5 OR Step6 (148353 Citations)

Step 7 (1826934 Citations)

"Child" [Mesh] OR "Maternal-Child Health Centers" [Mesh] OR "Child Nutrition Sciences" [Mesh] OR "Child Health Services" [Mesh] OR "Child Nutritional Physiological Phenomena" [Mesh] OR "Child Nutrition Disorders" [Mesh] OR "Child Mortality" [Mesh] OR "Child Welfare" [Mesh] OR "Child Care" [Mesh] OR "Child Reactive Disorders" [Mesh] OR "Child Guidance" [Mesh] OR "Child Reactive Disorders" [Mesh] OR "Child Behavior Disorders" [Mesh] OR "Child, Orphaned" [Mesh] OR "Child, Institutionalized" [Mesh] OR "Child, Hospitalized" [Mesh] OR "Child Development" [Mesh] OR "Child Behavior" [Mesh] OR "Developmental Disabilities" [Mesh] OR "Mental Disorders Diagnosed in Childhood" [Mesh] OR "Disabled Children" [Mesh] OR "children" [TIAB] OR "newborn*" [TIAB] OR "childhood" [TIAB] OR "baby" [TIAB] OR "babies" [TIAB] OR "toddler" [TIAB] OR "toddlers" [TIAB] OR "infants" [TIAB] OR "infant" [TIAB] OR "infantile" [TIAB] OR "young patient" [TIAB] OR "young patients" [TIAB] OR "Pediatric Nursing" [Mesh] OR "Pediatric Assistants" [Mesh] OR "Hospitals, Pediatric" [Mesh] OR "Intensive Care Units, Pediatric" [Mesh] OR "Pediatrics" [Mesh] OR "Pediatricians" [TIAB] OR "paediatricians" [TIAB] OR "Pediatrician" [TIAB] OR "paediatrician" [TIAB] OR "Pediatrics" [TIAB] OR "paediatrics" [TIAB] OR "Pediatric" [TIAB] OR "paediatric" [TIAB]

Step 1 OR (Step 2 AND 3) OR Step 4 OR Step 5 OR Step6 AND Step7 (24156 Citations)

EMBASE TE/ED

completed April 1, 2010 (20052 Citations)

Step 1 (39771 Citations)

'gastroenteritis'/exp OR 'gastroenteritis' OR 'protein losing gastroenteropathy'/exp OR 'protein losing gastroenteropathy' OR 'celiac disease'/exp OR 'celiac disease' OR 'tropical sprue'/exp OR 'tropical sprue' OR 'infantile gastroenteritis'/exp OR 'infantile gastroenteritis' OR 'acute gastroenteritis'/exp OR 'acute gastroenteritis' OR 'viral gastroenteritis'/exp OR 'viral gastroenteritis' OR 'persistent diarrhea' OR 'persistent diarrhoea' OR 'recurrent diarrhea' OR 'recurrent diarrhoea'

Step 2 (4062 Citations)

'intestine mucosa permeability'/exp OR 'small intestine absorption'/exp

Step 3 (745 Citations)

'environmental enteropathies' OR 'environmental enteropathy' OR 'tropical enteropathy' OR 'tropical enteropathies' OR 'tropical sprue'/exp OR 'tropical sprue' OR 'idiopathic tropical malabsorption syndromes' OR 'idiopathic tropical malabsorption syndrome'

OR

Step 4 (3611 citations)

('chronic disease'/exp AND 'diarrhea'/exp) OR 'chronic diarrhea'/exp

Step 5 (3156573 Citations)

'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR pediatr* OR paediatr* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*

(Step 1 OR Step 2 OR Step 3 OR Step 4) AND Step 5 (20052 Citations)

Global Health TE/ED

completed June 1, 2010 (7825 citations)

Step 1 (232244 Citations)

(child or children or newborn$ or childhood or baby or babies or toddler or toddlers or infants or infant or infantile or "young patients" or "young patient" or pediatrics or pediatric or paediatric or paediatrics or girls or sons or daughters or "child welfare" or "rearing practices" or unicef or paediatr$ or "child development" or "child nutrition" or "child health" or kid or kids or pediatricians or paediatricians).af.

Step 2 (4555 Citations)

(enteropathy or scouring).id. OR ("chronic infections" and diarrhoea).de. OR (diarrhea and "nutritional status").id. OR ("tropical sprue$" or "tropical enteropath$" or "environmental enteropath$" or "persistent diarrhea$" or "Persistent diarrhoea$" or "chronic diarrhoea$" or "chronic diarrhea$" or "intestinal inflamm*" or "intestinal permeability").af.

Step 3 (620850 Citations)

(undernutrition or "tropical countries" or "tropical zones" or "parasitic infections").id. or (tropics or "bacterial diseases").de. or (vv600 or vv210 or hh600 or ll822 or vv130).cc.

Step 4 (28447 Citations)

"("intestinal mucosa" or "small intestine" or "gastroenteritis" or intestines or "intestinal diseases" or "intestinal absorption").de. or (Intestines or "gastrointestinal tract").id.

Step 1 AND (Step 2 OR (Step 3 AND Step 4)) (10242 Citations)

Step 5 (*Journals indexed by PubMed and Embase removed) (2417 Citations)

"Journal of Pediatric Gastroenterology and Nutrition" [Journals] OR Journal of Clinical Microbiology" [Journals] OR"Archives of Disease in Childhood" [Journals] OR"Pediatric Infectious Disease Journal" [Journals] OR"Journal of Infectious Diseases" [Journals] OR"Journal of Pediatrics" [Journals] OR

"Clinical Infectious Diseases" [Journals] OR"Infection and Immunity" [Journals] OR

"Journal of Medical Virology" [Journals] OR"Transactions of the Royal Society of Tropical Medicine and Hygiene" [Journals] OR"Journal of Nutrition" [Journals] OR "East African Medical Journal" [Journals]

"BMC Infectious Diseases" [Journals] OR"American Journal of Tropical Medicine and Hygiene" [Journals] OR"Pediatric Research" [Journals] OR"Archives de Pediatrie" [Journals] OR

"Journal of Paediatrics and Child Health" [Journals] OR"Asian Pacific Journal of Allergy and Immunology" [Journals] OR"Journal of Tropical Pediatrics" [Journals]

Step 1 AND (Step 2 OR (Step 3 AND Step 4) NOT Step 5 (7825 Citations)

PubMed MalnutritIon

completed April 19, 2010 (23238 Citations)

Step 1 (2540333 Citations)

"developing country" [tiab] OR "developing countries" [tiab] OR "developing nation" [tiab] OR "developing nations" [tiab] OR "developing population" [tiab] OR "developing populations" [tiab] OR "developing world" [tiab] OR "less developed country" [tiab] OR "less developed countries" [tiab] OR "less developed nation" [tiab] OR "less developed nations" [tiab] OR "less developed population" [tiab] OR "less developed populations" [tiab] OR "less developed world" [tiab] OR "lesser developed country" [tiab] OR "lesser developed countries" [tiab] OR "lesser developed nation" [tiab] OR "lesser developed nations" [tiab] OR "lesser developed population" [tiab] OR "lesser developed populations" [tiab] OR "lesser developed world" [tiab] OR "under developed country" [tiab] OR "under developed countries" [tiab] OR "under developed nation" [tiab] OR "under developed nations" [tiab] OR "under developed population" [tiab] OR "under developed populations" [tiab] OR "under developed world" [tiab] OR "underdeveloped country" [tiab] OR "underdeveloped countries" [tiab] OR "underdeveloped nation" [tiab] OR "underdeveloped nations" [tiab] OR "underdeveloped population" [tiab] OR "underdeveloped populations" [tiab]

OR "underdeveloped world" [tiab] OR "middle income country" [tiab] OR "middle income countries" [tiab] OR "middle income nation" [tiab] OR "middle income nations" [tiab] OR "middle income population" [tiab] OR "middle income populations" [tiab] OR "low income country" [tiab] OR "low income countries" [tiab] OR "low income nation" [tiab] OR "low income nations" [tiab] OR "low income population" [tiab] OR "low income populations" [tiab] OR "lower income country" [tiab] OR "lower income countries" [tiab] OR "lower income nation" [tiab] OR "lower income nations" [tiab] OR "lower income population" [tiab] OR "lower income populations" [tiab] OR "underserved country" [tiab] OR "underserved countries" [tiab] OR "underserved nation" [tiab] OR "underserved nations" [tiab] OR "underserved population" [tiab] OR "underserved populations" [tiab] OR "underserved world" [tiab] OR "under served country" [tiab] OR "under served countries" [tiab] OR "under served nation" [tiab] OR "under served nations" [tiab] OR "under served population" [tiab] OR "under served populations" [tiab] OR "under served world" [tiab] OR "deprived country" [tiab] OR "deprived countries" [tiab] OR "deprived nation" [tiab] OR "deprived nations" [tiab] OR "deprived population" [tiab] OR "deprived populations" [tiab] OR "deprived world" [tiab] OR "poor country" [tiab] OR "poor countries" [tiab] OR "poor nation" [tiab] OR "poor nations" [tiab] OR "poor population" [tiab] OR "poor populations" [tiab] OR "poor world" [tiab] OR "poorer country" [tiab] OR "poorer countries" [tiab] OR "poorer nation" [tiab] OR "poorer nations" [tiab] OR "poorer population" [tiab] OR "poorer populations" [tiab] OR "poorer world" [tiab] OR "developing economy" [tiab] OR "developing economies" [tiab] OR "less developed economy" [tiab] OR "less developed economies" [tiab] OR "lesser developed economy" [tiab] OR "lesser developed economies" [tiab] OR "under developed economy" [tiab] OR "under developed economies" [tiab] OR "underdeveloped economy" [tiab] OR "underdeveloped economies" [tiab] OR "middle income economy" [tiab] OR "middle income economies" [tiab] OR "low income economy" [tiab] OR "low income economies" [tiab] OR "lower income economy" [tiab] OR "lower income economies" [tiab] OR "low gdp" [tiab] OR "low gnp" [tiab] OR "low gross domestic" [tiab] OR "low gross national" [tiab] OR "lower gdp" [tiab] OR "lower gnp" [tiab] OR "lower gross domestic" [tiab] OR "lower gross national" [tiab] OR lmic [tiab] OR lmics [tiab] OR "third world" [tiab] OR "lami country" [tiab] OR "lami countries" [tiab] OR "transitional country" [tiab] OR "transitional countries" [tiab] OR "developing country" [ot] OR "developing countries" [ot] OR "developing nation" [ot] OR "developing nations" [ot] OR "developing population" [ot] OR "developing populations" [ot] OR "developing world" [ot] OR "less developed country" [ot] OR "less developed countries" [ot] OR "less developed nation" [ot] OR "less developed nations" [ot] OR "less developed population" [ot] OR "less developed populations" [ot] OR "less developed world" [ot] OR "lesser developed country" [ot] OR "lesser developed countries" [ot] OR "lesser developed nation" [ot] OR "lesser developed nations" [ot] OR "lesser developed population" [ot] OR "lesser developed populations" [ot] OR "lesser developed world" [ot] OR "under developed country" [ot] OR "under developed countries" [ot] OR "under developed nation" [ot] OR "under developed nations" [ot] OR "under developed population" [ot] OR "under developed populations" [ot] OR "under developed world" [ot] OR "underdeveloped country" [ot] OR "underdeveloped countries" [ot] OR "underdeveloped nation" [ot] OR "underdeveloped nations" [ot] OR "underdeveloped population" [ot] OR "underdeveloped populations" [ot] OR "underdeveloped world" [ot] OR "middle income country" [ot] OR "middle income countries" [ot] OR "middle income nation" [ot] OR "middle income nations" [ot] OR "middle income population" [ot] OR "middle income populations" [ot] OR "low

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OR Guyana [pl] OR Haiti [pl] OR Honduras [pl] OR Hungary [pl] OR India [pl] OR Maldives [pl] OR Indonesia [pl] OR Iran [pl] OR Iraq [pl] OR Isle of Man [pl] OR Jamaica [pl] OR Jordan [pl] OR Kazakhstan [pl] OR Kazakh [pl] OR Kenya [pl] OR Kiribati [pl] OR Korea [pl] OR Kosovo [pl] OR Kyrgyzstan [pl] OR Kirghizia [pl] OR Kyrgyz Republic [pl] OR Kirghiz [pl] OR Kirgizstan [pl] OR "Lao PDR" [pl] OR Laos [pl] OR Latvia [pl] OR Lebanon [pl] OR Lesotho [pl] OR Basutoland [pl] OR Liberia [pl] OR Libya [pl] OR Lithuania [pl] OR Macedonia [pl] OR Madagascar [pl] OR Malagasy Republic [pl] OR Malaysia [pl] OR Malaya [pl] OR Malay [pl] OR Sabah [pl] OR Sarawak [pl] OR Malawi [pl] OR Nyasaland [pl] OR Mali [pl] OR Malta [pl] OR Marshall Islands [pl] OR Mauritania [pl] OR Mauritius [pl] OR Agalega Islands [pl] OR Mexico [pl] OR Micronesia [pl] OR Middle East [pl] OR Moldova [pl] OR Moldovia [pl] OR Moldovian [pl] OR Mongolia [pl] OR Montenegro [pl] OR Morocco [pl] OR Ifni [pl] OR Mozambique [pl] OR Myanmar [pl] OR Myanma [pl] OR Burma [pl] OR Namibia [pl] OR Nepal [pl] OR Netherlands Antilles [pl] OR New Caledonia [pl] OR Nicaragua [pl] OR Niger [pl] OR Nigeria [pl] OR Northern Mariana Islands [pl] OR Oman [pl] OR Muscat [pl] OR Pakistan [pl] OR Palau [pl] OR Palestine [pl] OR Panama [pl] OR Paraguay [pl] OR Peru [pl] OR Philippines [pl] OR Philipines [pl] OR Phillipines [pl] OR Phillippines [pl] OR Poland [pl] OR Portugal [pl] OR Puerto Rico [pl] OR Romania [pl] OR Rumania [pl] OR Roumania [pl] OR Russia [pl] OR Russian [pl] OR Rwanda [pl] OR Ruanda [pl] OR Saint Kitts [pl] OR St Kitts [pl] OR Nevis [pl] OR Saint Lucia [pl] OR St Lucia [pl] OR Saint Vincent [pl] OR St Vincent [pl] OR Grenadines [pl] OR Samoa [pl] OR Samoan Islands [pl] OR Navigator Island [pl] OR Navigator Islands [pl] OR Sao Tome [pl] OR Saudi Arabia [pl] OR Senegal [pl] OR Serbia [pl] OR Montenegro [pl] OR Seychelles [pl] OR Sierra Leone [pl] OR Slovenia [pl] OR Sri Lanka [pl] OR Ceylon [pl] OR Solomon Islands [pl] OR Somalia [pl] OR Sudan [pl] OR Suriname [pl] OR Surinam [pl] OR Swaziland [pl] OR Syria [pl] OR Tajikistan [pl] OR Tadzhikistan [pl] OR Tadjikistan [pl] OR Tadzhik [pl] OR Tanzania [pl] OR Thailand [pl] OR Togo [pl] OR Togolese Republic [pl] OR Tonga [pl] OR Trinidad [pl] OR Tobago [pl] OR Tunisia [pl] OR Turkey [pl] OR Turkmenistan [pl] OR Turkmen [pl] OR Uganda [pl] OR Ukraine [pl] OR Uruguay [pl] OR USSR [pl] OR Soviet Union [pl] OR Union of Soviet Socialist Republics [pl] OR Uzbekistan [pl] OR Uzbek OR Vanuatu [pl] OR New Hebrides [pl] OR Venezuela [pl] OR Vietnam [pl] OR Viet Nam [pl] OR West Bank [pl] OR Yemen [pl] OR Yugoslavia [pl] OR Zambia [pl] OR Zimbabwe [pl] OR Rhodesia [pl] OR Africa [tiab] OR Asia [tiab] OR Caribbean [tiab] OR West Indies [tiab] OR South America [tiab] OR Latin America [tiab] OR Central America [tiab] OR Afghanistan [tiab] OR Albania [tiab] OR Algeria [tiab] OR Angola [tiab] OR Antigua [tiab] OR Barbuda [tiab] OR Argentina [tiab] OR Armenia [tiab] OR Armenian [tiab] OR Aruba [tiab] OR Azerbaijan [tiab] OR Bahrain [tiab] OR Bangladesh [tiab] OR Barbados [tiab] OR Benin [tiab] OR Byelarus [tiab] OR Byelorussian [tiab] OR Belarus [tiab] OR Belorussian [tiab] OR Belorussia [tiab] OR Belize [tiab] OR Bhutan [tiab] OR Bolivia [tiab] OR Bosnia [tiab] OR Herzegovina [tiab] OR Hercegovina [tiab] OR Botswana [tiab] OR Brazil [tiab] OR Bulgaria [tiab] OR Burkina Faso [tiab] OR Burkina Fasso [tiab] OR Upper Volta [tiab] OR Burundi [tiab] OR Urundi [tiab] OR Cambodia [tiab] OR Khmer Republic [tiab] OR Kampuchea [tiab] OR Cameroon [tiab] OR Cameroons [tiab] OR Cameron [tiab] OR Camerons [tiab] OR Cape Verde [tiab] OR Central African Republic [tiab] OR Chad [tiab] OR Chile [tiab] OR China [tiab] OR Colombia [tiab] OR Comoros [tiab] OR Comoro Islands [tiab] OR Comores [tiab] OR Mayotte [tiab] OR Congo [tiab] OR Zaire [tiab] OR Costa Rica [tiab] OR Cote d'Ivoire [tiab] OR Ivory Coast [tiab] OR Croatia [tiab] OR Cuba [tiab] OR Cyprus [tiab] OR Czechoslovakia [tiab] OR Czech Republic [tiab] OR

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Byelarus [ot] OR Byelorussian [ot] OR Belarus [ot] OR Belorussian [ot] OR Belorussia [ot] OR Belize [ot] OR Bhutan [ot] OR Bolivia [ot] OR Bosnia [ot] OR Herzegovina [ot] OR Hercegovina [ot] OR Botswana [ot] OR Brazil [ot] OR Bulgaria [ot] OR Burkina Faso [ot] OR Burkina Fasso [ot] OR Upper Volta [ot] OR Burundi [ot] OR Urundi [ot] OR Cambodia [ot] OR Khmer Republic [ot] OR Kampuchea [ot] OR Cameroon [ot] OR Cameroons [ot] OR Cameron [ot] OR Camerons [ot] OR Cape Verde [ot] OR Central African Republic [ot] OR Chad [ot] OR Chile [ot] OR China [ot] OR Colombia [ot] OR Comoros [ot] OR Comoro Islands [ot] OR Comores [ot] OR Mayotte [ot] OR Congo [ot] OR Zaire [ot] OR Costa Rica [ot] OR Cote d'Ivoire [ot] OR Ivory Coast [ot] OR Croatia [ot] OR Cuba [ot] OR Cyprus [ot] OR Czechoslovakia [ot] OR Czech Republic [ot] OR Slovakia [ot] OR Slovak Republic [ot] OR Djibouti [ot] OR French Somaliland [ot] OR Dominica [ot] OR Dominican Republic [ot] OR East Timor [ot] OR East Timur [ot] OR Timor Leste [ot] OR Ecuador [ot] OR Egypt [ot] OR United Arab Republic [ot] OR El Salvador [ot] OR Eritrea [ot] OR Estonia [ot] OR Ethiopia [ot] OR Fiji [ot] OR Gabon [ot] OR Gabonese Republic [ot] OR Gambia [ot] OR Gaza [ot] OR "Georgia Republic" [ot] OR "Georgian Republic" [ot] OR Ghana [ot] OR Gold Coast [ot] OR Greece [ot] OR Grenada [ot] OR Guatemala [ot] OR Guinea [ot] OR Guam [ot] OR Guiana [ot] OR Guyana [ot] OR Haiti [ot] OR Honduras [ot] OR Hungary [ot] OR India [ot] OR Maldives [ot] OR Indonesia [ot] OR Iran [ot] OR Iraq [ot] OR Isle of Man [ot] OR Jamaica [ot] OR Jordan [ot] OR Kazakhstan [ot] OR Kazakh [ot] OR Kenya [ot] OR Kiribati [ot] OR Korea [ot] OR Kosovo [ot] OR Kyrgyzstan [ot] OR Kirghizia [ot] OR Kyrgyz Republic [ot] OR Kirghiz [ot] OR Kirgizstan [ot] OR "Lao PDR" [ot] OR Laos [ot] OR Latvia [ot] OR Lebanon [ot] OR Lesotho [ot] OR Basutoland [ot] OR Liberia [ot] OR Libya [ot] OR Lithuania [ot] OR Macedonia [ot] OR Madagascar [ot] OR Malagasy Republic [ot] OR Malaysia [ot] OR Malaya [ot] OR Malay [ot] OR Sabah [ot] OR Sarawak [ot] OR Malawi [ot] OR Nyasaland [ot] OR Mali [ot] OR Malta [ot] OR Marshall Islands [ot] OR Mauritania [ot] OR Mauritius [ot] OR Agalega Islands [ot] OR Mexico [ot] OR Micronesia [ot] OR Middle East [ot] OR Moldova [ot] OR Moldovia [ot] OR Moldovian [ot] OR Mongolia [ot] OR Montenegro [ot] OR Morocco [ot] OR Ifni [ot] OR Mozambique [ot] OR Myanmar [ot] OR Myanma [ot] OR Burma [ot] OR Namibia [ot] OR Nepal [ot] OR Netherlands Antilles [ot] OR New Caledonia [ot] OR Nicaragua [ot] OR Niger [ot] OR Nigeria [ot] OR Northern Mariana Islands [ot] OR Oman [ot] OR Muscat [ot] OR Pakistan [ot] OR Palau [ot] OR Palestine [ot] OR Panama [ot] OR Paraguay [ot] OR Peru [ot] OR Philippines [ot] OR Philipines [ot] OR Phillipines [ot] OR Phillippines [ot] OR Poland [ot] OR Portugal [ot] OR Puerto Rico [ot] OR Romania [ot] OR Rumania [ot] OR Roumania [ot] OR Russia [ot] OR Russian [ot] OR Rwanda [ot] OR Ruanda [ot] OR Saint Kitts [ot] OR St Kitts [ot] OR Nevis [ot] OR Saint Lucia [ot] OR St Lucia [ot] OR Saint Vincent [ot] OR St Vincent [ot] OR Grenadines [ot] OR Samoa [ot] OR Samoan Islands [ot] OR Navigator Island [ot] OR Navigator Islands [ot] OR Sao Tome [ot] OR Saudi Arabia [ot] OR Senegal [ot] OR Serbia [ot] OR Montenegro [ot] OR Seychelles [ot] OR Sierra Leone [ot] OR Slovenia [ot] OR Sri Lanka [ot] OR Ceylon [ot] OR Solomon Islands [ot] OR Somalia [ot] OR Sudan [ot] OR Suriname [ot] OR Surinam [ot] OR Swaziland [ot] OR Syria [ot] OR Tajikistan [ot] OR Tadzhikistan [ot] OR Tadjikistan [ot] OR Tadzhik [ot] OR Tanzania [ot] OR Thailand [ot] OR Togo [ot] OR Togolese Republic [ot] OR Tonga [ot] OR Trinidad [ot] OR Tobago [ot] OR Tunisia [ot] OR Turkey [ot] OR Turkmenistan [ot] OR Turkmen [ot] OR Uganda [ot] OR Ukraine [ot] OR Uruguay [ot] OR USSR [ot] OR Soviet Union [ot] OR Union of Soviet Socialist Republics [ot] OR Uzbekistan [ot] OR Uzbek OR Vanuatu [ot] OR New Hebrides [ot] OR Venezuela [ot] OR Vietnam [ot] OR Viet Nam [ot] OR West Bank [ot] OR

Yemen [ot] OR Yugoslavia [ot] OR Zambia [ot] OR Zimbabwe [ot] OR Rhodesia [ot] OR Developing Countries [Mesh:noexp] OR Africa [Mesh:noexp] OR Africa, Northern [Mesh:noexp] OR Africa South of the Sahara [Mesh:noexp] OR Africa, Central [Mesh:noexp] OR Africa, Eastern [Mesh:noexp] OR Africa, Southern [Mesh:noexp] OR Africa, Western [Mesh:noexp] OR Asia [Mesh:noexp] OR Asia, Central [Mesh:noexp] OR Asia, Southeastern [Mesh:noexp] OR Asia, Western [Mesh:noexp] OR Caribbean Region [Mesh:noexp] OR West Indies [Mesh:noexp] OR South America [Mesh:noexp] OR Latin America [Mesh:noexp] OR Central America [Mesh:noexp] OR Afghanistan [Mesh:noexp] OR Albania [Mesh:noexp] OR Algeria [Mesh:noexp] OR American Samoa [Mesh:noexp] OR Angola [Mesh:noexp] OR "Antigua and Barbuda" [Mesh:noexp] OR Argentina [Mesh:noexp] OR Armenia [Mesh:noexp] OR Azerbaijan [Mesh:noexp] OR Bahrain [Mesh:noexp] OR Bangladesh [Mesh:noexp] OR Barbados [Mesh:noexp] OR Benin [Mesh:noexp] OR Byelarus [Mesh:noexp] OR Belize [Mesh:noexp] OR Bhutan [Mesh:noexp] OR Bolivia [Mesh:noexp] OR Bosnia-Herzegovina [Mesh:noexp] OR Botswana [Mesh:noexp] OR Brazil [Mesh:noexp] OR Bulgaria [Mesh:noexp] OR Burkina Faso [Mesh:noexp] OR Burundi [Mesh:noexp] OR Cambodia [Mesh:noexp] OR Cameroon [Mesh:noexp] OR Cape Verde [Mesh:noexp] OR Central African Republic [Mesh:noexp] OR Chad [Mesh:noexp] OR Chile [Mesh:noexp] OR China [Mesh:noexp] OR Colombia [Mesh:noexp] OR Comoros [Mesh:noexp] OR Congo [Mesh:noexp] OR Costa Rica [Mesh:noexp] OR Cote d'Ivoire [Mesh:noexp] OR Croatia [Mesh:noexp] OR Cuba [Mesh:noexp] OR Cyprus [Mesh:noexp] OR Czechoslovakia [Mesh:noexp] OR Czech Republic [Mesh:noexp] OR Slovakia [Mesh:noexp] OR Djibouti [Mesh:noexp] OR "Democratic Republic of the Congo" [Mesh:noexp] OR Dominica [Mesh:noexp] OR Dominican Republic [Mesh:noexp] OR East Timor [Mesh:noexp] OR Ecuador [Mesh:noexp] OR Egypt [Mesh:noexp] OR El Salvador [Mesh:noexp] OR Eritrea [Mesh:noexp] OR Estonia [Mesh:noexp] OR Ethiopia [Mesh:noexp] OR Fiji [Mesh:noexp] OR Gabon [Mesh:noexp] OR Gambia [Mesh:noexp] OR "Georgia (Republic)" [Mesh:noexp] OR Ghana [Mesh:noexp] OR Greece [Mesh:noexp] OR Grenada [Mesh:noexp] OR Guatemala [Mesh:noexp] OR Guinea [Mesh:noexp] OR Guinea-Bissau [Mesh:noexp] OR Guam [Mesh:noexp] OR Guyana [Mesh:noexp] OR Haiti [Mesh:noexp] OR Honduras [Mesh:noexp] OR Hungary [Mesh:noexp] OR India [Mesh:noexp] OR Indonesia [Mesh:noexp] OR Iran [Mesh:noexp] OR Iraq [Mesh:noexp] OR Jamaica [Mesh:noexp] OR Jordan [Mesh:noexp] OR Kazakhstan [Mesh:noexp] OR Kenya [Mesh:noexp] OR Korea [Mesh:noexp] OR Kosovo [Mesh:noexp] OR Kyrgyzstan [Mesh:noexp] OR Laos [Mesh:noexp] OR Latvia [Mesh:noexp] OR Lebanon [Mesh:noexp] OR Lesotho [Mesh:noexp] OR Liberia [Mesh:noexp] OR Libya [Mesh:noexp] OR Lithuania [Mesh:noexp] OR Macedonia [Mesh:noexp] OR Madagascar [Mesh:noexp] OR Malaysia [Mesh:noexp] OR Malawi [Mesh:noexp] OR Mali [Mesh:noexp] OR Malta [Mesh:noexp] OR Mauritania [Mesh:noexp] OR Mauritius [Mesh:noexp] OR Mexico [Mesh:noexp] OR Micronesia [Mesh:noexp] OR Middle East [Mesh:noexp] OR Moldova [Mesh:noexp] OR Mongolia [Mesh:noexp] OR Montenegro [Mesh:noexp] OR Morocco [Mesh:noexp] OR Mozambique [Mesh:noexp] OR Myanmar [Mesh:noexp] OR Namibia [Mesh:noexp] OR Nepal [Mesh:noexp] OR Netherlands Antilles [Mesh:noexp] OR New Caledonia [Mesh:noexp] OR Nicaragua [Mesh:noexp] OR Niger [Mesh:noexp] OR Nigeria [Mesh:noexp] OR Oman [Mesh:noexp] OR Pakistan [Mesh:noexp] OR Palau [Mesh:noexp] OR Panama [Mesh:noexp] OR Papua New Guinea [Mesh:noexp] OR Paraguay [Mesh:noexp] OR Peru [Mesh:noexp] OR Philippines [Mesh:noexp] OR Poland [Mesh:noexp] OR Portugal

[Mesh:noexp] OR Puerto Rico [Mesh:noexp] OR Romania [Mesh:noexp] OR Russia [Mesh:noexp] OR "Russia (Pre-1917)" [Mesh:noexp] OR Rwanda [Mesh:noexp] OR "Saint Kitts and Nevis" [Mesh:noexp] OR Saint Lucia [Mesh:noexp] OR "Saint Vincent and the Grenadines" [Mesh:noexp] OR Samoa [Mesh:noexp] OR Saudi Arabia [Mesh:noexp] OR Senegal [Mesh:noexp] OR Serbia [Mesh:noexp] OR Montenegro [Mesh:noexp] OR Seychelles [Mesh:noexp] OR Sierra Leone [Mesh:noexp] OR Slovenia [Mesh:noexp] OR Sri Lanka [Mesh:noexp] OR Somalia [Mesh:noexp] OR South Africa [Mesh:noexp] OR Sudan [Mesh:noexp] OR Suriname [Mesh:noexp] OR Swaziland [Mesh:noexp] OR Syria [Mesh:noexp] OR Tajikistan [Mesh:noexp] OR Tanzania [Mesh:noexp] OR Thailand [Mesh:noexp] OR Togo [Mesh:noexp] OR Tonga [Mesh:noexp] OR "Trinidad and Tobago" [Mesh:noexp] OR Tunisia [Mesh:noexp] OR Turkey [Mesh:noexp] OR Turkmenistan [Mesh:noexp] OR Uganda [Mesh:noexp] OR Ukraine [Mesh:noexp] OR Uruguay [Mesh:noexp] OR USSR [Mesh:noexp] OR Uzbekistan [Mesh:noexp] OR Vanuatu [Mesh:noexp] OR Venezuela [Mesh:noexp] OR Vietnam [Mesh:noexp] OR Yemen [Mesh:noexp] OR Yugoslavia [Mesh:noexp] OR Zambia [Mesh:noexp] OR Zimbabwe [Mesh:noexp] OR "tropical climate" OR "tropical climate" [MeSH] OR "Vulnerable Populations" [Mesh] OR "American Native Continental Ancestry Group" [Mesh] OR "Oceanic Ancestry Group" [Mesh] OR "aboriginals" [all fields] OR "aboriginals" [all fields] OR "native americans" [all fields] OR "native american" [all fields] OR "first nations" [all fields] OR inuit [all fields] OR eskimo [all fields] OR eskimos [all fields] OR maori [all fields] OR "Health Services, Indigenous" [MeSH]

Step 2 (53847 Citations)

"Growth Disorders" [Mesh:NoExp] OR "Body Weight Changes" [Mesh] OR "Child Nutrition Disorders" [Mesh] OR "Infant Nutrition Disorders" [Mesh]

Step 1 AND Step 2 (7592 Citations)

Step 3 (73672 Citations)

"Failure to Thrive" [Mesh] OR "Body Height" [Mesh]OR "Thinness" [Mesh] OR "Starvation" [Mesh] OR "Protein Deficiency" [Mesh] OR "Malnutrition" [Mesh] OR "Malnutrition" [Mesh] or "stunting" [all fields] OR "stunted" [all fields] OR "wasted" [TIAB] OR "wasting" [TIAB] OR "height for age" [all fields] OR "weight for age" [all fields] OR "weight for height" [all fields] OR "growth faltering" [all fields] OR "underweight" [all fields] OR "under weight" [all fields] OR "short stature" [all fields]

(Step 1 AND Step 2) OR Step 3 (79085 Citations)

Step 4 (1848948 Citations)

'Child' [Mesh] OR 'Maternal-Child Health Centers' [Mesh] OR 'Child Nutrition Sciences' [Mesh] OR 'Child Health Services' [Mesh] OR 'Child Nutritional Physiological Phenomena' [Mesh] OR 'Child Nutrition Disorders' [Mesh] OR 'Child Mortality' [Mesh] OR 'Child Welfare' [Mesh] OR 'Child Care' [Mesh] OR 'Child Reactive Disorders' [Mesh] OR 'Child Guidance' [Mesh] OR 'Child Reactive Disorders' [Mesh] OR 'Child Behavior Disorders' [Mesh] OR 'Child, Orphaned' [Mesh]

OR 'Child, Institutionalized' [Mesh] OR 'Child, Hospitalized' [Mesh] OR 'Child Development' [Mesh] OR 'Child Behavior' [Mesh] OR 'Developmental Disabilities' [Mesh] OR 'Mental Disorders Diagnosed in Childhood' [Mesh] OR 'Disabled Children' [Mesh] OR 'children' [TIAB] OR 'newborn*' [TIAB] OR 'childhood' [TIAB] OR 'baby' [TIAB] OR 'babies' [TIAB] OR 'toddler' [TIAB] OR 'toddlers' [TIAB] OR 'infants' [TIAB] OR 'infant' [TIAB] OR 'infantile' [TIAB] OR 'young patient' [TIAB] OR 'young patients' [TIAB] OR 'Pediatric Nursing' [Mesh] OR 'Pediatric Assistants' [Mesh] OR 'Hospitals, Pediatric' [Mesh] OR 'Intensive Care Units, Pediatric' [Mesh] OR 'Pediatrics' [Mesh] OR 'Pediatricians' [TIAB] OR 'paediatricians' [TIAB] OR 'Pediatrician' [TIAB] OR 'paediatrician' [TIAB] OR 'Pediatrics' [TIAB] OR 'paediatrics' [TIAB] OR 'Pediatric' [TIAB] OR 'paediatric' [TIAB]

Step 4 AND ((Step 1 AND Step 2) OR Step 3(34445 Citations))

Step 5 (2329420 Citations)

"Congenital Abnormalities" [Mesh] OR "Genetic Diseases, Inborn" [Mesh] OR "Endocrine System Diseases" [Mesh]OR "Hormones, Hormone Substitutes, and Hormone Antagonists" [Mesh] OR "Kidney Diseases" [Mesh]

(Step 4 AND ((Step 1 AND Step 2) OR Step 3)) NOT Step 5 23238 Citations

EMBASE Malnutrition

completed April 19, 2010 (17,634 Citations)

Step 1 (3,164,283 citations)

'child'/exp OR 'child' OR 'children'/exp OR 'children' OR 'youth'/exp OR 'youth' OR youth* OR newborn* OR 'newborn'/exp OR 'newborn' OR 'new born' OR 'childhood disease'/exp OR 'childhood disease' OR 'baby'/exp OR 'baby' OR babies OR 'infant'/exp OR 'infant' OR infant* OR childhood* OR toddler* OR kid OR kids OR 'young patient' OR boy* OR girl* OR 'young age' OR pediatr* OR paediatr* OR 'child death'/exp OR 'child death' OR 'child health'/exp OR 'child health' OR 'child care'/exp OR 'child care' OR 'childhood mortality'/exp OR 'childhood mortality' OR 'child hospitalization'/exp OR 'child hospitalization' OR 'pediatric hospital'/exp OR 'pediatric hospital' OR child*

Step 2 (4,437,122 Citations)

Afghanistan or Albania or Algeria or Angola or Antigua or Barbuda or Argentina or Armenia or Armenian or Aruba or Azerbaijan or Bahrain or Bangladesh or Barbados or Benin or Byelarus or Byelorussian or Belarus or Belorussian or Belorussia or Belize or Bhutan or Bolivia or Bosnia or Herzegovina or Hercegovina or Botswana or Brazil or Bulgaria or 'Burkina Faso' or 'Burkina Fasso' or 'Upper Volta' or Burundi or Urundi or Cambodia or 'Khmer Republic' or Kampuchea or Cameroon or Cameroons or Cameron or Camerons or 'Cape Verde' or 'Central African

Republic' or Chad or Chile or China or Colombia or Comoros or 'Comoro Islands' or Comores or Mayotte or Congo or Zaire or 'Costa Rica' or 'Cote d Ivoire' or 'Ivory Coast' or Croatia or Cuba or Cyprus or Czechoslovakia or 'Czech Republic' or Slovakia or 'Slovak Republic' or Djibouti or 'French Somaliland' or Dominica or 'Dominican Republic' or 'East Timor' or 'East Timur' or 'Timor Leste' or Ecuador or Egypt or 'United Arab Republic' or 'El Salvador' or Eritrea or Estonia or Ethiopia or Fiji or Gabon or 'Gabonese Republic' or Gambia or Gaza or 'Georgia Republic' or 'Georgian Republic' or Ghana or 'Gold Coast' or Greece or Grenada or Guatemala or Guinea or Guam or Guiana or Guyana or Haiti or Honduras or Hungary or India or Maldives or Indonesia or Iran or Iraq or Jamaica or Jordan or Kazakhstan or Kazakh or Kenya or Kiribati or Korea or Kosovo or Kyrgyzstan or Kirghizia or Kyrgyz or Kirghiz or Kirgizstan or 'Lao PDR' or Laos or Latvia or Lebanon or Lesotho or Basutoland or Liberia or Libya or Lithuania or Macedonia or Madagascar or Malagasy or Malaysia or Malaya or Malay or Sabah or Sarawak or Malawi or Nyasaland or Mali or Malta or 'Marshall Islands' or Mauritania or Mauritius or 'Agalega Islands' or Mexico or Micronesia or 'Middle East' or Moldova or Moldovia or Moldovian or Mongolia or Montenegro or Morocco or Ifni or Mozambique or Myanmar or Myanma or Burma or Namibia or Nepal or 'Netherlands Antilles' or 'New Caledonia' or Nicaragua or Niger or Nigeria or 'Mariana Islands' or Oman or Muscat or Pakistan or Palau or Palestine or Panama or Paraguay or Peru or Philippines or Philipines or Phillipines or Phillippines or Poland or Portugal or 'Puerto Rico' or Romania or Rumania or Roumania or Russia or Russian or Rwanda or Ruanda or 'Saint Kitts' or 'St Kitts' or Nevis or 'Saint Lucia' or 'St Lucia' or 'Saint Vincent' or 'St Vincent' or Grenadines or Samoa or 'Samoan Islands' or 'Navigator Island' or 'Navigator Islands' or 'Sao Tome' or 'Saudi Arabia' or Senegal or Serbia or Montenegro or Seychelles or 'Sierra Leone' or Slovenia or 'Sri Lanka' or Ceylon or 'Solomon Islands' or Somalia or Sudan or Suriname or Surinam or Swaziland or Syria or Tajikistan or Tadzhikistan or Tadjikistan or Tadzhik or Tanzania or Thailand or Togo or Togolese or Tonga or Trinidad or Tobago or Tunisia or Turkey or Turkmenistan or Turkmen or Uganda or Ukraine or Uruguay or USSR or 'Soviet Union' or 'Union of Soviet Socialist Republics' or Uzbekistan or Uzbek or Vanuatu or 'New Hebrides' or Venezuela or Vietnam or 'Viet Nam' or 'West Bank' or Yemen or Yugoslavia or Zambia or Zimbabwe or Rhodesia OR ((developing or 'less developed' or 'under developed' or underdeveloped or 'middle income' or 'low income' or 'lower income' or underserved or 'under served' or deprived or poor*) and (countr* or nation* or population* or world)) OR ((developing or 'less developed' or 'lesser developed' or 'under developed' or underdeveloped or middle income or 'lower income' or 'lower income') AND (economy or economies)) OR (low* NEAR (gdp or gnp or gross domestic or gross national)) OR (low NEAR/3 middle) OR (lmic OR lmics OR third AND world OR 'lami countries' OR 'lami country') OR (transitional AND countr*) OR 'tropic climate'/exp OR 'aborigine'/exp OR 'American Indian'/exp OR 'Eskimo'/exp OR 'Maori'/exp OR 'indigenous people'/exp

Step 3 (141,231 Citations)

'thinness' OR 'stunted' OR 'stunting' OR 'growth faltering' OR 'wasted' OR 'height for age' OR 'weight for age' OR 'weight for height' OR 'underweight' OR 'under weight' OR 'growth failure' OR 'protein deficiency'/exp OR 'starvation'/exp OR 'underweight'/exp OR 'lean body weight'/exp OR 'weight change'/exp OR 'growth curve'/exp OR 'growth inhibition'/exp OR 'growth rate'/exp OR 'postnatal growth'/exp OR 'failure to thrive'/exp OR 'wasting syndrome'/exp OR 'malnutrition'/de or 'developmental, age and growth parameters'/de OR 'growth disorder'/de OR 'body height'/exp OR 'body height'/exp

Step 1 AND Step 2 AND Step 3 (24,575 Citations)

Step 4

'genetic and familial disorders'/exp OR 'congenital disorder'/exp OR 'endocrine disease'/exp OR 'hormones and agents acting on the endocrine system'/exp OR 'urogenital tract disease'/exp OR 'neoplasm'/exp

(Step 1 AND Step 2 AND Step 3) NOT Step 4 (16,833 Citations)

Step 5 (13,130 Citations)

'growth retardation'/exp

Step 1 and Step 2 and Step 5 (2,321 Citations)

Step 6 (5,6000,005)

'genetic and familial disorders'/exp OR 'congenital disorder'/exp OR 'hormones and agents acting on the endocrine system'/exp OR 'urogenital tract disease'/exp OR 'neoplasm'/exp

(Step 1 and Step 2 and Step 3) NOT Step 6 (801 Citations)

((Step 1 AND Step 2 AND Step 3) NOT Step 4) OR ((Step 1 and Step 2 and Step 5) NOT Step 6) (17,634 Citations)

WHO LILACS Database (TE/ED and Malnutrition)

completed June 17, 2010 (1617 Citations)

("tropical sprue" OR "tropical enteropathy" OR "environmental enteropathy" OR "persistent diarrhea" OR "Persistent diarrhoea" or "chronic diarrhoea" or "chronic diarrhea" OR "tropical malabsorption syndrome" OR Stunting OR wasting OR underweight OR "height for age" OR "weight for height" OR "weight for age" OR malnutrition) and (Child OR Children OR newborn OR childhood OR baby OR babies OR toddler OR toddlers OR infants OR infant OR infantile OR young patient OR young patients OR Pediatricians OR paediatricians OR Pediatrician OR paediatrician OR Pediatrics OR paediatrics OR Pediatric OR paediatric)

WHO SE Asia Database (IMSEAR) (TE/ED and Malnutrition)

completed June 17, 2010 (1335 Citations)

(("tropical sprue" OR "tropical enteropathy" OR "environmental enteropathy" OR "persistent diarrhea" OR "Persistent diarrhoea" or "chronic diarrhoea" or "chronic diarrhea" OR "tropical malabsorption syndrome" OR Stunting OR wasting OR underweight OR "height for age" OR "weight for height" OR "weight for age" OR malnutrition) AND (Child OR Children OR newborn

OR childhood OR baby OR babies OR toddler OR toddlers OR infants OR infant OR infantile OR young patient OR young patients OR Pediatricians OR paediatricians OR Pediatrician OR paediatrician OR Pediatrics OR paediatrics OR Pediatric OR paediatric))

WHO Western Pacific Region Index Medicus (WPRIM) (TE/ED and Malnutrition)

completed June 17, 2010 (685 Citations)

"tropical sprue" OR "tropical enteropathy" OR "environmental enteropathy" OR "persistent diarrhea" OR "Persistent diarrhoea" or "chronic diarrhoea" or "chronic diarrhea" OR "tropical malabsorption syndrome" OR Stunting OR wasting OR underweight OR "height for age" OR "weight for height" OR "weight for age" OR malnutrition

WHO EMRO (IMEMR) (TE/ED and Malnutrition)

completed June 17, 2010 (459 Citations)

Child OR Children OR newborn OR childhood OR baby OR babies OR toddler OR toddlers OR infants OR infant OR infantile OR young patient OR young patients OR Pediatricians OR paediatricians OR Pediatrician OR paediatrician OR Pediatrics OR paediatrics OR Pediatric OR paediatric [KeyWords] and "tropical sprue" OR "tropical enteropathy" OR "environmental enteropathy" OR "persistent diarrhea" OR "Persistent diarrhoea" or "chronic diarrhoea" or "chronic diarrhea" OR "tropical malabsorption syndrome" OR Stunting OR wasting OR underweight OR "height for age" OR "weight for height" OR "weight for age" OR malnutrition [KeyWords]

WHO African Index Medicus (TE/ED and Malnutrition)

completed June 17, 2010 (70 Citations)

"tropical sprue" OR "tropical enteropathy" OR "environmental enteropathy" OR "persistent diarrhea" OR "Persistent diarrhoea" or "chronic diarrhoea" or "chronic diarrhea" OR "tropical malabsorption syndrome" OR Stunting OR wasting OR underweight OR "height for age" OR "weight for height" OR "weight for age" OR malnutrition

Appendix 2. References used to test systematic search.

These papers were used to confirm inclusiveness in search criteria, and to confirm that filters do not inadvertently exclude relevant work.

Reference	Setting and why selected
Brown KH, Khatun M, Ahmed G. Relationship of the xylose absorption status of children in Bangladesh to their absorption of macronutrients from local diets. Am J Clin Nut. 1981;34(8):1540-7.	Setting: Bangladesh Reason for selection: Biomarker and physiologic test studied
Fagundes-Neto U, Viaro T, Wehba J, Patrício FR, Machado NL. Tropical enteropathy (environmental enteropathy) in early childhood: a syndrome caused by contaminated environment. J Trop Pediatr. 1984;30(4):204-9.	Setting: Brazil Reason for selection: Biomarkers, pathophysiologic correlates
Solomons NW, Mazariegos M, Brown KH, Klasing K. The underprivileged, developing country child: environmental contamination and growth failure revisited. Nutr Rev 1993;51(11):327-32.	Setting: Review Reason for selection: Addresses pathophysiology and epidemiology
Fagundes-Neto U, Martins MC, Lima FL, Patricio FR, Toledo MR. Asymptomatic environmental enteropathy among slum-dwelling infants. J Am Coll Nutr 1994;13(1):51-6.	Setting: Brazil Reason for selection: Pathophysiology
Bhutta ZA, Hendricks KM. Nutritional management of persistent diarrhea in childhood: a perspective from the developing world. J Pediatr Gastroenterol Nutr 1996;22(1):17-37.	Setting: Review Reason for selection: Therapy and epidemiology
Menzies IS, Zuckerman MJ, Nukajam WS, Somasundaram SG, Murphy B, Jenkins AP, et al. Geography of intestinal permeability and absorption. Gut 1999;44(4):483-9[1].	Setting: Qatar Reason for selection: Pathophysiology
Campbell DI, Elia M, Lunn PG. Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation. J Nutr. 2003;133(5):1332-8.	Setting: Gambia Reason for selection: Biomarkers related to stunting
Kukuruzovic R, Brewster DR, Gray E, Anstey NM. Increased nitric oxide production in acute diarrhoea is associated with abnormal gut permeability, hypokalaemia and malnutrition in tropical Australian aboriginal children. Trans R Soc Trop Med Hyg. 2003;97(1):115-20.	Setting: Australian Aboriginal children Reason for selection: Relates a relevant biomarker (NO production) to lactulose/rhamnose test of intestinal permeability
Solomons NW. Environmental contamination and chronic inflammation influence human growth potential. J Nutr 2003;133(5):1237[2].	Setting: Commentary Reason for selection: Risk factors

[1] The reference was not captured in the umbrella search of multiple databases with both TE/ED and stunting search terms (i.e., PubMed + EMBASE + GH—TE/ED + stunting).
[2] The reference was captured in the PubMed stunting search but lost when the child filter was added.

Reference	Setting and why selected
Campbell DI, McPhail G, Lunn PG, Elia M, Jeffries DJ. Intestinal inflammation measured by fecal neopterin in Gambian children with enteropathy: association with growth failure, *Giardia lamblia*, and intestinal permeability. J Pediatr Gastroenterol Nutr. 2004;39(2):153-7.	Setting: Gambia Reason for selection: Marker of gut inflammation in children and inflammation is related to another biomarker (lactulose:mannitol ratio) and growth of children in study
Salazar-Lindo E, Allen S, Brewster DR, Elliott EJ, Fasano A, Phillips AD, et al. Intestinal infections and environmental enteropathy: Working Group report of the second World Congress of Pediatric Gastroenterology, Hepatology, and Nutrition. J Pediatr Gastroenterol Nutr 2004;39 Suppl 2:S662-9.	Setting: Review Reason for selection: Broadly inclusive of topics of interest
Lima AA, Brito LF, Ribeiro HB, Martins MC, Lustosa AP, Rocha EM, et al. Intestinal barrier function and weight gain in malnourished children taking glutamine supplemented enteral formula. J Pediatr Gastroenterol Nutr 2005;40(1):28-35.	Setting: Brazil Reason for selection: Pathophysiology and treatment
Bhutta ZA. Effect of infections and environmental factors on growth and nutritional status in developing countries. J Pediatr Gastroenterol Nutr 2006;43 Suppl 3:S13-21[3].	Setting: Review Reason for selection: Epidemiology and causative factors
Bhutta ZA, Nelson EA, Lee WS, Tarr PI, Zablah R, Phua KB, et al. Recent advances and evidence gaps in persistent diarrhea. J Pediatr Gastroenterol Nutr 2008;47(2):260-5.	Setting: Review Reason for selection: Broadly inclusive data
Botero-Garcés JH, García-Montoya GM, Grisales-Patiño D, Aguirre-Acevedo DC, Alvarez-Uribe MC. *Giardia intestinalis* and nutritional status in children participating in the complementary nutrition program, Antioquia, Colombia, May to October 2006.Rev Inst Med Trop Sao Paulo. 2009;51(5):155-62.	Setting: Colombia Reason for selection: Studies relation between a specific agent and nutritional status
Goto R, Mascie-Taylor CG, Lunn PG. Impact of intestinal permeability, inflammation status and parasitic infections on infant growth faltering in rural Bangladesh 2009:Br J Nutr. 2009;101(10):1509-16.	Setting: Rural Bangladesh Reason for selection: Biomarkers associated with stunting
Humphrey JH. Child undernutrition, tropical enteropathy, toilets, and handwashing. Lancet 2009;374(9694):1032-5.	Setting: Review Reason for selection: Environmental factors
Ritchie BK, Brewster DR, Davidson GP, Tran CD, McNeil Y, Hawkes JS, et al. 13C-sucrose breath test: novel use of a noninvasive biomarker of environmental gut health. Pediatrics. 2009;124(2):620-6.	Setting: Australian Aboriginal children Reason for selection: Novel biomarker (exhaled isotope) to test intestinal permeability

[3] The reference was captured in the search with only the stunting term.

Appendix 3. Summary of sampled references published between 1990-1999.

Method: An index of records determined to be relevant to this systematic review was sorted by year. From this ordering, every 10th article was sampled.

1. Khoshoo V, Bhan MK, Jain R, Jayashree S, Bhandari N, Sazawal S, et al. Intestinal glucoamylase and other disaccharidases in children with protracted diarrhoea. Indian J Med Res. 1990;92:1-4.
Sample size: 42 (all < 5 years of age)
Subjects: Persistent or chronic diarrhea and malnutrition
Markers: Jejunal biopsy, brush border disaccharidase activity, and correlation of latter with degree of mucosal injury
Relevance to 2000-2010 set: Disaccharidase activity was investigated in one study from the previous decade; this study adds assessment of its relationship with histology.

2. Saavedra JM, Brown KH. Nonabsorbable marker and single, random stool samples used for measuring intestinal absorption of macronutrients in infants and children. Am J Clin Nutr. 1991;53(3):790-94.
Sample size: 21 (all < 5 years of age)
Subjects: Malnourished
Markers: Fecal excretion of polyethylene glycol as a marker of intestinal absorption and in comparison to standard balance test
Relevance to 2000-2010 set: These tests of absorption were not included in the previous decade article set.

3. Sullivan PB, Lunn PG, Northrop-Clewes C, Crowe PT, Marsh MN, Neale G. Persistent diarrhea and malnutrition--the impact of treatment on small bowel structure and permeability. J Pediatr Gastroenterol Nutr. 1992;14(2):208-15.
Sample size: 20 (all < 5 years of age)
Subjects: Persistent or chronic diarrhea, most also malnourished
Markers: Lactulose and mannitol fractional excretion, L:M, and jejunal biopsy; compared L:M with biopsy results
Relevance to 2000-2010 set: The L:M test was reported in 25 studies in later decade, but none compared it to histology.

4. Baqui AH, Sack RB, Black RE, Chowdhury HR, Yunus M, Siddique AK. Cell-mediated immune deficiency and malnutrition are independent risk factors for persistent diarrhea in Bangladeshi children. Am J Clin Nutr. 1993;58(4):543-48.
Sample size: 705 (all < 5 years of age)
Subjects: Persistent diarrhea, malnutrition, or asymptomatic
Markers: Cell-mediated immune response with multiple-antigen skin test
Relevance to 2000-2010 set: A similar study was published in the 2000-2010 publication set.

5. Roy SK, Akramuzzaman SM, Haider R, Khatun M, Akbar MS, Eeckels R. Persistent diarrhoea: efficacy of a rice-based diet and role of nutritional status in recovery and nutrient absorption. Br J Nutr. 1994;71(1):123-34.
Sample size: 51 (all < 5 years of age)
Subjects: Persistent diarrhea (many also malnourished) and controls with previous history of acute diarrhea
Markers: Comparison of nutrient absorption in cases and controls determined by 72-hour balance study and recovery of cases following rice-based diet therapy
Relevance to 2000-2010 set: The 72 hour balance study was not reported in studies reviewed from the later decade.

6. Kallas MR, Patricio FR, Fagundes-Neto U. [Morphometrics of the small intestine in children with diarrhea due to classical enteropathogenic Escherichia coli and to environmental asymptomatic enteropathy]. Rev Assoc Med Bras. 1995;41(3):162-166. Portuguese.
Sample size: 46 (likely most or all subjects < 5 years of age; mean age was under 7 months)
Subjects: Acute or persistent diarrhea with stool culture positive for EPEC (cases) or asymptomatic children negative for EPEC (controls)
Markers: Small intestine biopsy and morphometry
Relevance to 2000-2010 set: Histology was examined in 18 studies in the 2000-2010 set with one study also using morphometric assessment.

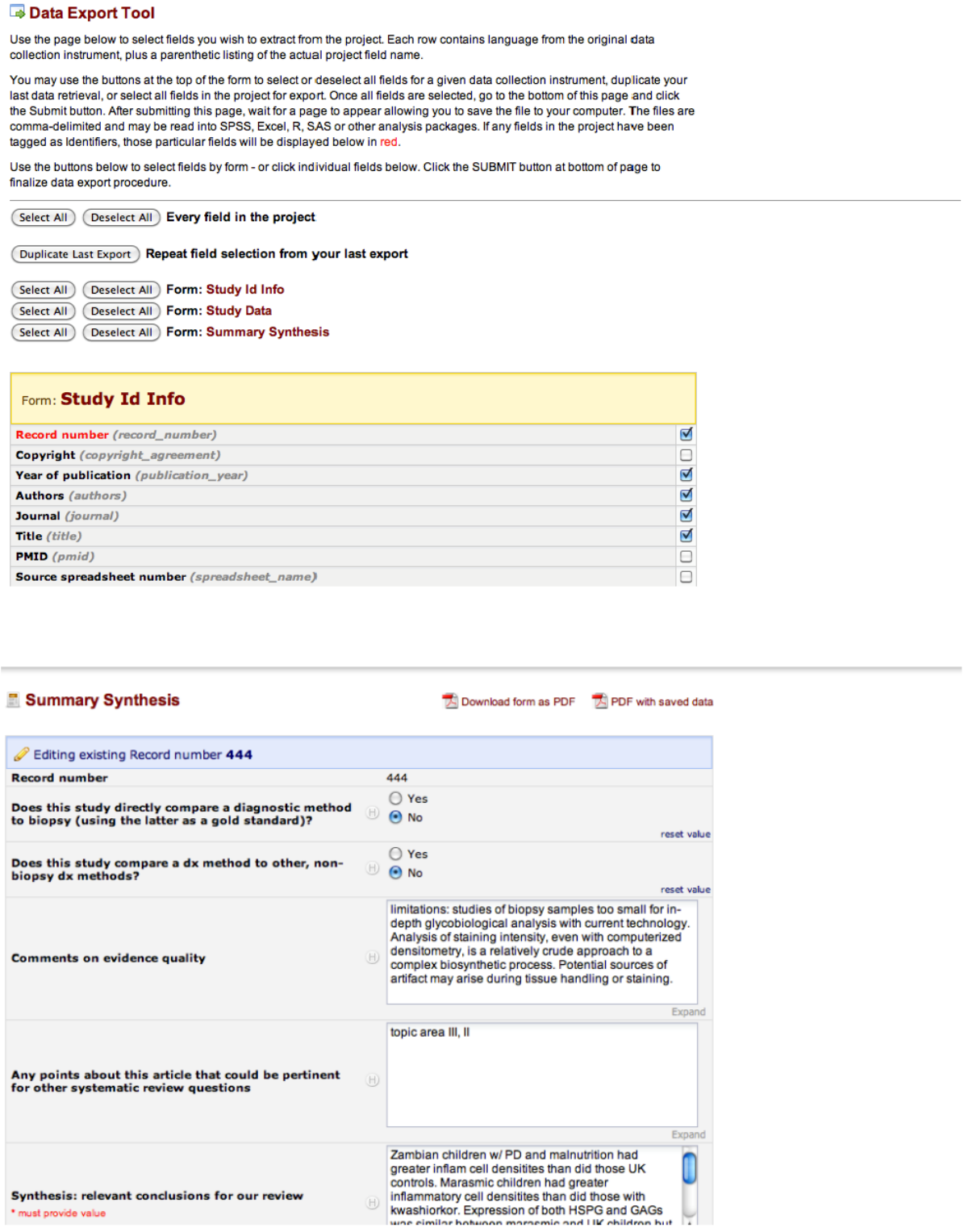
7. Cooper ES, Ramdath DD, Whyte-Alleng C, Howell S, Serjeant BE. Plasma proteins in children with trichuris dysentery syndrome. J Clin Pathol. 1997;50(3):236-240.
Sample size: 89 (many older than 5 years of age)
Subjects: Chronic diarrhea with and without *Trichuris* dysentery syndrome and healthy controls
Markers: Blood markers: alpha-1-antitrypsin, ceruloplasmin, albumin, globulin, fibrinogen, fibronectin, ferritin, transferrin, plasma viscosity, hemoglobin, leukocytes, and CRP
Relevance to 2000-2010 set: Primarily assessed markers of systemic inflammation that were reviewed in assessments of articles from the previous decade. The remaining markers are primarily assessments of hepatic function and were not assessed in the 2000-2010 set.

8. Brooks SE, Reid WA. Scanning electron microscopy of the jejunum in children with protein-energy malnutrition. West Indian Med J. 1997;46(1):15-21.
Sample size: 7 (all < 5 years of age)
Subjects: Fatal severe kwashiorkor or marasmic kwashiorkor
Markers: Scanning electron microscopy (SEM) and light microscopy on jejunal biopsy sections taken by autopsy and fixed within 75 minutes after death
Relevance to 2000-2010 set: In the later decade publications, SEM and light microscopy were used in one study to investigate jejunal morphology in 16 infants with persistent diarrhea, many of whom also had small bowel bacterial overgrowth (as measured by jejunal secretion) and/or exhibited some degree of malnutrition.

9. Abbas KA, Bilal R, Sajjad MI, Latif Z, Mirza NH. Fat absorption in persistent diarrhoea using 13C-labelled trioctanoin breath test. J Trop Pediatr. 1999;45(2):87-94.
Sample size: 10 (all < 5 years of age)
Subjects: Persistent diarrhea (some with malnutrition) and asymptomatic controls
Markers: Fat absorption by breath test after ^{13}C-labelled trioctanoin administration
Relevance to 2000-2010 set: 2 studies in the 1990-1999 publication set assessed fat absorption although not by breath test with this specific medium chain fatty acid.

10. Taniguchi K, Rikimaru T, Yartey JE, Akpedonu P, Armar-Klemesu MA, Nkrumah FK, et al. Immunological background in children with persistent diarrhea in Ghana. Pediatr Int. 1999;41(2):162-167.
Sample size: 85 (all < 5 years of age)
Subjects: Persistent or acute diarrhea
Markers: A variety of serum markers of systemic inflammation and immune response were compared between persistent and acute diarrhea cases, including: albumin, pre-albumin, total protein, transferrin, IgA & IgG subclass fractions, natural killer cells, lymphocyte immunophenotypes, and T-cell activation.
Relevance to 2000-2010 set: Many of these systemic markers were examined in the 2000-2010 set, although some were not.

Appendix 4. Sample REDCap template.



Data Export Tool

Use the page below to select fields you wish to extract from the project. Each row contains language from the original data collection instrument, plus a parenthetic listing of the actual project field name.

You may use the buttons at the top of the form to select or deselect all fields for a given data collection instrument, duplicate your last data retrieval, or select all fields in the project for export. Once all fields are selected, go to the bottom of this page and click the Submit button. After submitting this page, wait for a page to appear allowing you to save the file to your computer. The files are comma-delimited and may be read into SPSS, Excel, R, SAS or other analysis packages. If any fields in the project have been tagged as Identifiers, those particular fields will be displayed below in red.

Use the buttons below to select fields by form - or click individual fields below. Click the SUBMIT button at bottom of page to finalize data export procedure.

Select All | Deselect All — **Every field in the project**

Duplicate Last Export — **Repeat field selection from your last export**

Select All | Deselect All — **Form: Study Id Info**
Select All | Deselect All — **Form: Study Data**
Select All | Deselect All — **Form: Summary Synthesis**

Form: **Study Id Info**

Record number *(record_number)*	☑
Copyright *(copyright_agreement)*	☐
Year of publication *(publication_year)*	☑
Authors *(authors)*	☑
Journal *(journal)*	☑
Title *(title)*	☑
PMID *(pmid)*	☐
Source spreadsheet number *(spreadsheet_name)*	☐

Summary Synthesis

Download form as PDF | PDF with saved data

Editing existing Record number **444**

Record number	444
Does this study directly compare a diagnostic method to biopsy (using the latter as a gold standard)?	○ Yes ◉ No — reset value
Does this study compare a dx method to other, non-biopsy dx methods?	○ Yes ◉ No — reset value
Comments on evidence quality	limitations: studies of biopsy samples too small for in-depth glycobiological analysis with current technology. Analysis of staining intensity, even with computerized densitometry, is a relatively crude approach to a complex biosynthetic process. Potential sources of artifact may arise during tissue handling or staining. — Expand
Any points about this article that could be pertinent for other systematic review questions	topic area III, II — Expand
Synthesis: relevant conclusions for our review * must provide value	Zambian children w/ PD and malnutrition had greater inflam cell densitites than did those UK controls. Marasmic children had greater inflammatory cell densitites than did those with kwashiorkor. Expression of both HSPG and GAGs was similar between marasmic and UK children but

Appendix 5. Highly considered but excluded references.

Reference	Country	Reason for exclusion
Altuntas B, Filik B, Ensari A, Zorlu P, Teziç T. Can zinc deficiency be used as a marker for the diagnosis of celiac disease in Turkish children with short stature? Pediatr Int. 2000;42(6):682-684.	Turkey	Biopsy data were the same as previously reported in a 1998 publication[1] that was included in this review. This 2000 publication adds no new data of relevance to this review.
Bahia M, Rabello A, Brasileiro Filho G, Penna FJ. Serum antigliadin antibody levels as a screening criterion before jejunal biopsy indication for celiac disease in a developing country. Braz J Med Biol Res. 2001;34(11):1415-1420.	Brazil	The only outcomes of interest to this review that were reported on for subjects of interest (controls that did not have celiac disease) were that their jejunal biopsy results were "normal," and no other data or specific information was reported that pertained to this review.
Bay A, Oner AF, Celebi V, Uner A. Evaluation of vitamin K deficiency in children with acute and intractable diarrhea. Adv Ther. 2006;23(3):469-474.	Turkey	Outcomes were primarily related to micronutrient (vitamin K) deficiency or malabsorption.
Cooke ML, Goddard EA, Brown RA. Endoscopy findings in HIV-infected children from sub-Saharan Africa. J Trop Pediatr. 2009;55(4):238-243.	South Africa	Most subjects had upper gastrointestinal conditions that were not of interest to this review. Only 3 subjects had diarrhea, and it was unlikely that they were all under 5 yr.
Kelly P, Musuku J, Kafwembe E, Libby G, Zulu I, Murphy J, et al. Impaired bioavailability of vitamin A in adults and children with persistent diarrhoea in Zambia. Aliment Pharmacol Ther. 2001;15(7):973-979.	Zambia	Change in serum retinol status was assessed following administration of oral vitamin A to adult cases (males hospitalized with persistent diarrhea (PD)) (n=15), controls (males hospitalized with conditions other than PD) (n=24) and cases under 2 yr hospitalized with PD and malnutrition (n=11). While the children with PD did have similar degrees of change in serum retinol after vitamin A administration compared to the adult controls, the study did not include childhood controls. Without childhood controls and with limited sample size of children, interpretation and generalization of findings to childhood enteric function is limited.
Kukuruzovic R, Robins-Browne RM, Anstey NM, Brewster DR. Enteric pathogens, intestinal permeability and nitric oxide	Australia	Data on outcomes of interest to this review were not reported.

[1] Altuntas B, Kansu A, Ensari A, Girgin N. Celiac disease in Turkish short-statured children and the value of antigliadin antibody in diagnosis. Acta Paediatr Jpn. 1998;40(5):457-460.

Reference	Country	Reason for exclusion
production in acute gastroenteritis. Pediatr Infect Dis J. 2002;21(8):730-739.		
Kumar R, Marwaha N, Marwaha RK, Garewal G. Vitamin K deficiency in diarrhoea. Indian J Pediatr. 2001;68(3):235-238.	India	Outcomes were primarily related to micronutrient (vitamin K) deficiency or malnutrition.
Manary MJ, Hotz C, Krebs NF, Gibson RS, Westcott JE, Arnold T, et al. Dietary phytate reduction improves zinc absorption in Malawian children recovering from tuberculosis but not in well children. J Nutr. 2000;130(12):2959-2964.	Malawi	Subjects ranged in age from 3-13 yr, but based on the group means and standard deviations for age, there were likely to be few subjects under age 5 years.
Thacher TD, Obadofin MO, O'Brien KO, Abrams SA. The effect of vitamin D2 and vitamin D3 on intestinal calcium absorption in Nigerian children with rickets. J Clin Endocrinol Metab. 2009;94(9):3314-3321.	Nigeria	Study assessed differences in calcium uptake with varying vitamin D preparations and was not an assessment of intestinal function.
Ukarapol N, Lertprasertsuk N, Fuchs GJ, Wongsawasdi L, Sirisanthana V. Impact of gastrointestinal endoscopy on HIV-infected children. Dig Endosc. 2004;16(1):26-29.	Thailand	Study described 13 colonoscopy or sigmoidoscopy and 10 gastroduodenoscopy sessions for 14 patients resulting in 7 possible assessments of the small intestine. However results were aggregated across gastrointestinal anatomical sites, and it was difficult to extract results of interest to this review.
Walkowiak J, Herzig KH. Fecal elastase-1 is decreased in villous atrophy regardless of the underlying disease. Eur J Clin Invest. 2001;31(5):425-430.	Poland	The age range of all subjects (n=54) was 2-16 yr with a mean of 7.0 yr, SE=0.5. The sample size of children of any age with presentations of interest to this review was n=18. The high mean age of subjects coupled with small sample size suggest that few children with presentations meeting inclusion criteria were likely under 5 yr. In addition, it was unclear if the study setting met developing country setting inclusion criteria.
Yachha SK, Aggarwal R, Srinivas S, Srivastava A, Somani SK, Itha S. Antibody testing in Indian children with celiac disease. Indian J Gastroenterol. 2006;25(3):132-135.	India	While some subjects in this study were under 5 yr of age, the subjects of interest to this review (i.e., the children without celiac disease who had small intestinal biopsies) were all aged $\geq$5 yr.

Appendix 6. Review articles with information of relevance to the systematic review.

Bhatnagar S. Laboratory diagnosis of persistent and chronic diarrhea. IJPP. 2003;5(2):125-132.
Bhutta ZA, Nelson EA, Lee WS, Tarr PI, Zablah R, Phua KB, et al. Recent advances and evidence gaps in persistent diarrhea. J Pediatr Gastroenterol and Nutr. 2008;47(2):260-265.
Bhutta ZA. Effect of infections and environmental factors on growth and nutritional status in developing countries. J Pediatr Gastroenterol Nutr. 2006 Dec;43: Suppl 3:S13-21.
Bickler SW. Tropical enteropathy protects against Western diseases in environments of poor sanitation. Med Hypotheses. 2006;67(1):146-150.
Brewster DR. Critical appraisal of the management of severe malnutrition: 3. Complications. J Paediatr Child Health. 2006;42(10):583-593.
Brewster DR, Manary MJ, Menzies IS, O'Loughlin EV, Henry RL. Intestinal permeability in kwashiorkor. Arch Dis Child. 1997; Mar;76(3):236-41.
Butler RN. Non-invasive tests in animal models and humans: a new paradigm for assessing efficacy of biologics including prebiotics and probiotics. Curr Pharm Des. 2008;14(14):1341-50.
Davidson G, Kritas S, Butler R. Stressed mucosa. Nestle Nutr Workshop Ser Pediatr Program. 2007;59:133-142; discussion 143-146.
Gibbons T, Fuchs GJ. Chronic enteropathy: clinical aspects. Nestle Nutr Workshop Ser Pediatr Program. 2007;59:89-101; discussion 102-104.
Guerrant RL, Oriá RB, Moore SR, Oriá MO, Lima AA. Malnutrition as an enteric infectious disease with long-term effects on child development. Nutr Rev. 2008;66(9):487-505.
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Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments

2003
 	
Alcantara CS et al.
 	
Interleukin-8, tumor necrosis factor-alpha, and lactoferrin in immunocompetent hosts with experimental and Brazilian children with acquired cryptosporidiosis
 	
Fecal cytokines and lactoferrin as markers of intestinal inflammation among children with and without *Cryptosporidium parvum*.
	Fortaleza, Brazil
	
	3-43 mo olds recruited from a shantytown community who were screened for enteric pathogens.
	
	There was a high prevalence of malnutrition among the cases.
	
	(Adults experimentally exposed to *C. parvum* by ingestion were also studied; these data were not included in this review.)
		Case-control
		
		n=32;
		
		n=17 cases with *C. parvum:*
		• 4 with no diarrhea
		• 10 with AD
		• 3 with PD
		
		n=15 controls with no diarrhea or enteric pathogens and comparable HAZ and WAZ scores to cases
			<u>Stool tests</u>:
			• Lactoferrin (17 cases and 15 controls tested)
			• IL-8 (13 cases and 15 controls tested)
			• TNF-α (10 cases and 0 controls tested)
				Lactoferrin positive:
				• 12/17 cases
				  • 1/4 cases without diarrhea
				  • 8/10 AD cases
				  • 3/3 PD cases
				• 3/15 controls (p=0.006 compared to cases)
				
				IL-8 detectable:
				• 3/13 all cases
				  • 0/2 cases without diarrhea
				  • 3/10 AD cases
				  • 0/1 PD cases
				• 6/16 controls (p=0.435 compared to cases)
				
				TNF-α detectable:
				• 0/10 cases
					The proportion of children who tested positive for fecal lactoferrin was greater in those with cryptosporidiosis, especially those symptomatic with diarrhea, than in uninfected controls, although 20% of the control group tested positive.
					
					Fecal IL-8 did not differ between those with and without *Cryptosporidium* infection. TNF-α was not elevated among children with *Cryptosporidium* infection.
						Direct comparisons between various stool tests were not reported.
						
						Lactoferrin results were graded based on agglutination reaction positivity with increasing dilution and were considered negative if there was no reaction at 1:25.
						
						Four subjects were breastfed and were tested for lactoferrin.

2002 Alves GM et al. Nutritional status and breath hydrogen test with lactose and lactulose in Terena Indian children Lactose hydrogen breath test (HBT) as a marker of lactase activity, and lactulose HBT as a marker of	Limão Verde and Córrego Seco, Mato Grosso du Sul, Brazil All children <10 yr old were recruited from these rural villages.	Cross-sectional n=264; <5 yr old: n=145 (However results were provided by <4 and ≥4 yr old age groups.)	<u>Breath Tests</u>: • Lactose HBT (251 tested) • Lactulose HBT (252 tested)	Lactose HBT: • Elevated: 27.1% among all subjects • Borderline: 43.0% among all subjects • 0% of subjects <4 yr had elevated or borderline results Lactulose HBT positive: • 11.5% of all subjects • 8.6% of subjects <4 yr	The prevalence of lactase deficiency as measured by lactose HBT was >25%, but non-existent among those <4 yr of age. Prevalence of SBBO as assessed by lactulose HBT was ~10%.	Assessment of association between lactulose and lactose absorption was not reported.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
SBBO						

2009
 	
Amadi B et al.
 	
Reduced production of sulfated glycosaminoglycans occurs in Zambian children with kwashiorkor but not marasmus
 	
Duodenal biopsy including assessments of intestinal markers in children with PD and different forms of malnutrition
	Lusaka, Zambia
	
	12.2-19.8 mo olds with PD and malnutrition admitted to the malnutrition ward of a teaching hospital.
		Case-control
		
		n=41*;
		
		n=41 cases with PD and malnutrition:
		• 18 with marasmus
		• 8 with marasmic kwashiorkor
		• 15 with kwashiorkor
		
		n=19 healthy control children from UK
		
		* UK subjects are presented in this table due to comparisons of interest made in the review. However we do not include these subjects in the sample size for this review.
			<u>Endoscopic duodenal biopsy:</u>
			• Histopathology
			• Densities in lamina propria and crypt epithelium:
			  • Cell proteins:
			  • Glycosaminoglycan (GAG)
			  • Enterocyte heparan sulfate proteoglycan (HSPG)
			  • Syndecan-1
			• Inflammatory cell markers:
			  • CD3 IEL
			  • Ki67
			  • Human leukocyte antigen DR-1 (HLA-DR)
				Biopsy findings among the Zambian compared to the UK children:
				• Villous height reduced
				• Crypt depth increased
				• ~50% reduction in crypt:villous ratio
				• Values for lamina propria cell densities were not reported for UK subjects
				
				No significant differences in crypt or villous measures or lamina propria cell densities were observed between nutritional groups or after nutritional rehabilitation.
				
				Intestinal markers:
				• Inflammatory markers were seen in higher densities compared to the UK children. There were significant differences between the different nutritional groups in the specific types of inflammatory markers.
				• There was a significant reduction in GAGs and HSPG in the kwashiorkor group compared to UK children, but no significant differences between kwashiorkor and other presentations of malnutrition.
				• There was no difference in
					Mucosal architecture was markedly abnormal compared to UK controls but did not vary between marasmus and kwashiorkor presentations of malnutrition.
					
					Inflammatory cell densities were generally higher compared to UK children and showed different patterns across the malnutrition presentations.
					
					Tissue concentrations of HSPG and GAG were reduced especially amongst children with kwashiorkor. Intestinal protein markers did not differ amongst the malnutrition groups.
						27 subjects were HIV positive; incidence was lower in the kwashiorkor group.

Appendix 7. Evidence table of all studies included in the review.

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				epithelial syndecan-1 protein expression between the malnutrition groups (data not available for UK controls).		

2000
 	
Azim T et al.
 	
Immune response of Bangladeshi children with acute diarrhea who subsequently have persistent diarrhea
 	
Immune activation tests, as well as transferrin and albumin as markers of nutritional status among children with and without PD
	Dhaka, Bangladesh
	
	7-12 mo olds with 6-8 days of watery diarrhea attending the International Centre for Diarrheal Disease Research.
	
	Cases were those who went on to develop PD, controls were those who did not.
	
	An additional group of subjects without diarrhea were recruited from a nutrition follow-up unit.
	
	Prevalence of malnutrition was high in all groups.
		Case-control
		
		n=136;
		
		n=38 cases with PD
		
		n=98 controls:
		• 85 with AD
		• 13 with no diarrhea
			<u>Blood tests:</u>
			• IFN-γ
			• TNF-α
			• WBC (total and differential)
			• IgA
			• IgG
			• IgM
			• Transferrin
			• Albumin
			• Immune function tests:
			  • Neutrophil polarization response to chemotactic factor
			  • Neutrophil opsonization to yeast
			  • Mononuclear cell proliferation, spontaneous and in response to stimuli with mitogens
			
			<u>Skin Test:</u>
			• Delayed-type hypersensitivity response (DTH) to tuberculin, tetanus, diphtheria, *Streptococcus, Proteus, Candida,* and *Trichophyton*
				WBC total and differential, immunoglobulin subtypes, cytokines, transferrin, and albumin did not differ between cases with diarrhea or controls, nor did stool leukocyte or erythrocyte counts.
				
				The percentages of neutrophils that polarized in response to stimulation were significantly higher in subjects with AD or PD compared to those without diarrhea; there was no difference between the two diarrhea groups.
				
				Opsonization did not vary between any groups.
				
				Monocyte spontaneous proliferation counts were less than half among children with no diarrhea compared to those with AD ($p<0.001$) or with PD ($p=0.011$); there was no difference between the two diarrhea groups.
				
				Monocyte proliferation in response to stimulation did not differ between the 3 groups.
				
				The proportion with DTH
					Some immune and inflammatory markers were associated with acute and/or persistent diarrhea.
					
					The only marker that was significantly associated with progression to PD was a negative DTH response to tuberculin antigen (odds ratio=3.8, CI: 1.4, 9.9). This was calculated from a logistic regression analysis that only included children with diarrhea.
						The number of controls was relatively small and their nutritional status was not reported.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
			Stool tests: • Leukocytes • Red blood cells	responses differed among the three groups only in response to tuberculin (p=0.021). More PD subjects had a negative tuberculin response than did subjects with AD (p=0.024).		
2005 Bhatnagar S et al. Celiac disease with mild to moderate histological changes is a common cause of chronic diarrhea in Indian children Duodenal biopsy among children with chronic diarrhea	Delhi, India 1-18 yr olds with a presentation consistent with CD (combination of chronic diarrhea, abdominal distension, and growth failure), recruited from a pediatric gastroenterology clinic. Subjects negative for CD-specific antibodies were of interest for this review.	Case-series n=107	Endoscopic duodenal biopsy: Histopathology	70 had normal histology (defined as crypt:villous ratio 1:2-3, absence of lymphoid lamina propria infiltration, and minimal intraepithelial lymphocytes (IEL). 37 had mild changes (defined as mild blunting of villi with crypt:villous ratio of 1:1*). A specific etiology was identified in only n=5: • 2 with giardiasis • 1 with lymphangiectasia • 2 with chronic pancreatitis Only children with CD had moderate or severe histologic changes. * Along with increased IEL and lymphocytic lamina propria infiltration.	More than one quarter of children with chronic diarrhea had normal small intestinal mucosa; at follow-up their growth had improved and their diarrhea had resolved. No definitive diagnosis was reached for 86% of subjects with abnormal histology (albeit most had mild findings).	
2003 Bitarakwate E et al. Serum zinc status of children with persistent diarrhea admitted to the diarrhea management unit of Mulago Hospital, Uganda	Kampala and Mpigi, Uganda 6-36 mo olds with PD, recruited from hospital, and healthy controls recruited mainly from the local population.	Case-control n=192; n=96 cases with PD n=96 healthy controls	Blood Tests: • Albumin • Total protein • Hemoglobin	PD cases: • 47.9% low serum protein • 69.7% low serum albumin • Low mean hemoglobin (10.5 g/dL) For controls, means of all three laboratory values were within normal range; percent of subjects with abnormal values are not reported.	Decreased albumin, serum total protein and hemoglobin concentrations were associated with PD.	

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
Serum protein, albumin, and hemoglobin among children with and without PD				All three test results were significantly lower in children with PD than in controls ($p< 0.01$ for each comparison).		
2010 Bukhari AS et al. DNA damage and plasma homocysteine concentrations are associated with serum metabolites and mineral constituents' profiles in children with persistent diarrhea Serum proteins, metabolites, and levels of DNA damage among children with and without PD	Faisalabad, Pakistan 3-6 yr olds admitted to hospital with PD and healthy controls.	Case-control n=72; n=36 cases with PD n=36 healthy controls	<u>Blood Tests</u>: Serum proteins and metabolites: • Albumin • Globulin • Homocysteine • Total protein • Total cholesterol, HDL, LDL, triglycerides • AST, ALT • T3, T4 • Total oxidant status (TOS), Total anti-oxidant status (TAS), and thiobarbituric reactive substances (TBARS) • DNA damage to lymphocytes	Mean values significantly higher among PD cases than in healthy controls: • LDL • Homocysteine • TOS • TBARs • DNA damage Mean values significantly lower among PD cases than in healthy controls: • Total protein • T4 • TAS	Multiple serum markers were associated with PD, especially DNA damage to lymphocytes ($p=0.0001$). The authors speculate that zinc deficiency, more commonly found in the children with PD, might be responsible for increased homocysteine concentrations and play an important role in mediating DNA damage.	Control recruitment strategy was not well described. TOS, TBARS and TAS were incompletely defined. Some values differed by gender in both the case and control groups: • Triglycerides • Total cholesterol • HDL • T3 Multiple markers studied; analyses did not appear to address potential confounding.
2007 Bushen OY et al. Heavy cryptosporidial infections in children in northeast Brazil: comparison of	Goncalves Dias favela in Fortaleza, Brazil All newborns from an urban shantytown were recruited at birth	Cohort n=42 (41 tested) Stools were collected at	<u>Stool Test</u>: Lactoferrin	68.3% were lactoferrin-positive; there were no differences in positivity between subjects with *C. hominis* and *C. parvum* spp. 67.9% of lactoferrin-positive subjects had very high titers.	Lactoferrin was correlated with younger age and symptomatic infection among those infected with *C. parvum.*	Lactoferrin results were graded based on agglutination reaction positivity with increasing dilution and

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
Cryptosporidium hominis and *Cryptosporidium parvum* Fecal lactoferrin as a marker of intestinal inflammation in children with *Cryptosporidium*	and followed for up to 4 yr. This study included only children testing positive for *Cryptosporidium.*	regular intervals as well as during episodes of diarrhea.		Younger children were more often lactoferrin-positive (p=0.03). The difference was mediated by *C. parvum;* 87.5% of ≤1 year olds compared to 40.0% of older children with *C. parvum* were lactoferrin-positive (p=0.04). There was no difference among those infected with *C. hominis.* Lactoferrin was correlated with symptomatic infection among those with *C. parvum*: 78.6% of symptomatic children compared to no asymptomatic children had a positive test (r=0.67, p=0.004[1]). Lactoferrin was not correlated with degree of oocyst shedding (p=0.28). Lactoferrin was correlated with ΔHAZ score among those with *C. parvum*, although this observation was not statistically significant (r=-0.39, p=0.13).	Lactoferrin did not significantly predict growth outcomes. *Cryptosporidium* species-specific differences were observed in lactoferrin results. In contrast to *C. parvum*, there was no association between lactoferrin and symptomatic / asymptomatic *C. hominis* infection (p=0.231). In addition, similar proportions of asymptomatic children with *C. hominis* had high fecal lactoferrin titers as had undetectable results.	were considered negative if there was no reaction at 1:50 and highly positive at >1:400. Data were part of a larger study; similar data on lactoferrin in *Giardia*-infected children was published by A. Kohli, et al. (also included in this review), using a slightly different grading scale for reporting lactoferrin results [133]. Rather than exclude breastfed children, Bushen et al. stratified results on breastfeeding status and found no difference in positive/ negative results, including when examined among younger and older children.

[1] Reported results were adjusted for confounding variables, unless otherwise noted.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments

2003
 	
Bustos M et al.
 	
Disaccharidase deficiency in Bolivian children with persistent diarrhea
 	
Jejunal biopsy and disaccharidase activities in children with PD and different forms of malnutrition
	Cochabamba, Bolivia
	
	3-34 mo old Amerindians hospitalized with PD and moderate or severe malnutrition in an urban setting.
		Cohort
		
		n=42 cases with PD and malnutrition:
		• 2 with kwashiorkor
		• 20 with marasmus
		• 20 with marasmic-kwashiorkor
		
		Children were assessed on admission and at three weeks, after diarrhea had resolved and anthropometrics were improving.
			<u>Jejunal tethered capsule biopsy:</u>
			• Histopathology
			• Disaccharidase activity:
			  • Lactase
			  • Sucrose-Isomaltase
			  • Maltase
			
			Histology was scored on a scale of 1 (normal) to 4 (severe morphological damage or flat mucosa).
				Most subjects had mild to moderate (score of 2-3) histological abnormalities, with one kwashiorkor patient having completely flat villi.
				
				Second biopsy showed a trend of improved mucosa, but difference was not significant based on histology score, intraepithelial lymphocyte density, or degree of infiltration of lamina propria.
				
				Percentages with enzymatic activity below normal at baseline, discharge:
				• Lactase: 64%, 59%
				• Sucrase-isomaltase: 97%, 90%
				• Maltase: 45%, 52%
				All changes were statistically significant.
				
				Lactase recovery was associated with admission HAZ (p=0.05) and WAZ (p=0.03) scores.
				
				Despite continued high disaccharidase deficiency prevalence at discharge, all children tolerated the lactose-containing formula challenge.
					Patients had diminished intestinal disaccharidase activity and substantial pathology on biopsy at admission and at three weeks, despite clinical improvements and tolerance of lactose-containing formula.	Spanish language article.
						
						Values for subnormal disaccharidase activity were not provided.
						
						The magnitude of lactase inverse association with growth parameters was not reported. Authors did not report whether they had tested for associations between maltase or sucrose-isomaltase and growth parameters.

2004 Campbell DI et al.	Keneba, Gambia 2 mo olds from rural area followed	Cohort n=72	<u>Stool Test</u>: Neopterin	Mean neopterin concentration was negatively correlated with long-term height (r=-0.29, p<0.009) and weight	L:M and mean fecal neopterin concentration were not correlated.	Study population might have some overlap with that

Appendix 7. Evidence table of all studies included in the review.

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Intestinal inflammation measured by fecal neopterin in Gambian children with enteropathy: association with growth failure*, Giardia lamblia*, and intestinal permeability Fecal neopterin and L:M as markers of intestinal inflammation and permeability, respectively, and their correlation with growth status and *Giardia* recovery in the stool	until 15 mo of age.	Subjects were evaluated with twice-weekly questionnaire to determine diarrhea morbidity, clinic assessments of growth, and screening laboratory tests every 2 mo.	Urine Tests: • Lactulose[2] • Mannitol • L:M	(r=-0.36, p<0.007) gain, but not with giardiasis. Mean[3] L:M (CI): 0.31 (0.26, 0.34). Mean excretion of lactulose (CI): 0.20 (0.18, 0.23). Mean excretion of mannitol (CI): 3.0 (2.8, 3.2). Mean L:M was negatively correlated with long-term height gain (r value not provided, p<0.0001), but was not correlated with presence of *Giardia.* L:M and fecal neopterin were not correlated (p=0.11).	Mean L:M in the Gambian children was substantially higher than normal values in children in the UK. These high L:M ratios appear to be driven by mannitol excretion.	of Campbell et al. also included in this review [110].
2003 Campbell DI et al. Growth faltering in rural Gambian infants is associated with impaired small intestinal barrier function, leading to endotoxemia and systemic inflammation L:M as a marker of intestinal permeability	Keneba, The Gambia All 2-11 mo olds were recruited from this rural village and followed up to 14 mo of age.	Cohort n=71	Urine Tests: • Lactulose[4] (53 tested) • Mannitol (52 tested) • L:M (52 tested) Blood tests: • Albumin • CBC • C-reactive protein (CRP) • IgA	At 8 wk of age: • Mean[5] L:M: 0.169 (CI: 0.145, 0.198; range: 0.058-0.657) • Mean lactulose recovery: 0.202 (SD=0.159; range: 0.009-0.640) • Mean mannitol recovery: 3.80 (SD=2.35; range: 0.52-8.58) L:M more than doubled between 12 wk-1 yr of age (r=0.44, p<0.001) and was driven by both increasing	Mean L:M ratios were elevated at 8 weeks of age, and more than doubled in the first year of life. Many markers of inflammation and endotoxin release were significantly correlated with L:M and lactulose recovery.	Presence of malaria parasites was assessed by blood smear at each study visit; the only parameter associated with malaria was CRP. Authors did not report investigating

[2] Lactulose and mannitol results were expressed as % of dose administered.
[3] Type of mean not specified.
[4] For lactulose and mannitol results, excretion measurement was not specified.
[5] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
and its relationship with various inflammatory markers and endotoxin			• IgM • IgG • Plasma endotoxin • IgG endotoxin-core antibody	lactulose (r=0.18, p<0.001) and decreasing mannitol (r=-0.14, p<0.01) excretion with age. WAZ and HAZ scores were negatively correlated with L:M (r=-0.41, p<0.001), and primarily driven by lactulose excretion (r=-0.39, p<0.001). Laboratory values were consistent with chronic, low level immunostimulation: • 50% of platelet and 39% of leukocyte counts were elevated, especially mean lymphocyte counts which were almost twice expected values [198]. • While the mean[6] CRP was within the normal range, 25% of values were above the upper limit of normal (5 mg/L), and 17% were >10 mg/L [198]. • Mean IgG, IgA and IgM concentrations were near normal at 8 wk of age, but increased rapidly; all three were elevated above expected values in all other age groups [198, 199]. • Mean[7] free plasma endotoxin concentration was twice the upper limit of normal [200] and IgG endotoxin-core antibody concentrations were also	Poor growth was significantly correlated with L:M ratios, primarily due to lactulose excretion. Authors postulate that while general markers of inflammation cannot be specifically ascribed to a gut source, endotoxin and its related core antibody are potentially a direct measure of intestinal inflammation due to gut gram negatives as a primary source of endotoxin release among subjects without sources of extra-intestinal gram negative infection.	relationships between certain serum parameters (blood counts, CRP concentrations) and L:M. Study population might have overlap with that of Campbell et al. 2004 also included in this review [15].

[6] Geometric mean.
[7] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				elevated [198]. • However, mean albumin concentrations (and concentrations within SD) were generally within normal range [198]. L:M was correlated with IgG and IgA (r=0.41 and 0.41, respectively, p<0.001), and IgM (r=0.28, p<0.02). IgG and IgA were also correlated with lactulose recovery (r=0.26 and 0.25, respectively, p<0.02). IgG endotoxin core antibody concentration was correlated with L:M and driven by lactulose recovery, (r=0.35, p<0.005 for both). Endotoxin concentrations were correlated with lactulose recovery (r=0.36, p<0.02) only.		
2003 Campbell DI et al. Chronic T cell-mediated enteropathy in rural west African children: relationship with nutritional status	Fajara and Sibanar, The Gambia 6 mo-3 yr old hospital- and clinic-based cases from rural communities.	Case-control n=40 cases: • Group 1: n=4 • Group 2: n=11 (7 with diarrhea) • Group 3: n=25 (18	<u>Endoscopic small bowel biopsy, site not specified</u>: • Histopathology • Morphometric assessment by computer analysis* • Intestinal tissue cytokines and	Crypt-hyperplasia and villous atrophy were observed among all Gambian subjects, and the degree of histopathology did not differ among cases with differing nutritional status, nor was there a correlation with diarrhea.	All Gambian subjects had evidence of enteropathy with crypt-hyperplasia and villous atrophy, and mean IELs >2 SD above UK norms,	Statistical methodology was not sufficiently detailed to determine what was compared (e.g. type of central tendency

Appendix 7. Evidence table of all studies included in the review.

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and small bowel function L:M as a marker of intestinal permeability, small bowl biopsy with assessment of intestinal immune markers, and computerized morphometric analysis among rural Gambian children with differing degrees of malnutrition and compared to well-nourished UK children	Case groups based on differences in nutritional status: 1. WAZ score >-2, with GI complaints other than diarrhea 2. Grade I protein energy malnutrition (PEM) (WAZ score -2 to -4) and unresponsive to nutritional supplements, with or without diarrhea 3. Grade II PEM (WAZ score <-4) with or without diarrhea Controls from UK* who were well nourished children with GI complaints other than diarrhea and with normal endoscopy results were also studied. * UK subjects are presented in this	with diarrhea) n=34 with case tissue samples sufficient for cytokine immunoreactivity tests: • Group 1: n=3 • Group 2: n=8 • Group 3: n=23	immune markers: • CD-3 • CD-4 • CD-8 • CD-19 • CD-25 • HLA-DR • Perforin • γδ T-cell receptor • Syndecan-1 • TNF-α • IFN-γ • TGF-β • IL-10 <u>Urine Tests</u>: • Lactulose[8] • Mannitol • L:M * Biopsy involved morphometric assessment by computer analysis of villous height, crypt depth, villous:crypt ratio, and intraepithelial lymphocyte (IEL) density (per 100 epithelial cells).	IEL[9] means were ~3-fold higher in Gambian than UK children. Median CD3, CD4, CD8, CD19, and CD25 cell counts were significantly higher (2-5x higher) among each case group compared to the UK controls. IEL, γδ, syndecan-1, HLA-DR, and perforin were detected among the Gambian children in varying degrees but were not reported for UK controls. Syndecan, CD3, and CD8 displayed a gradient proportional to malnutrition severity. All Gambian groups showed higher lamina propria cytokine-immunoreactive mononuclear cell density (~200-450/mm^2) than UK controls (30-80/mm^2). Among subjects with elevated cytokines, similar densities were seen for both pro-inflammatory (IFN-γ and TNF-α) and putative regulatory (IL-10 and TGF-β) cytokines. Epithelial expression of TGF-β was also enhanced compared to UK controls, but subjects with	independent of nutritional status and diarrhea history. Elevation of cell-mediated intestinal markers and mucosal proinflammatory cytokines was present across the 3 Gambian groups, variably correlated with nutritional status. L:M ratios were elevated in all Gambian groups, without apparent correlation to host nutritional status.	measure and variance calculations for L:M not stated). Duration of diarrhea not specified, but assumed to be persistent. Mucosal lymphocyte densities, cytokine immunoreactivity, and L:M results were not stratified by history of diarrhea.

[8] Lactulose and mannitol results were expressed as % of dose administered.
[9] These figures are presumed to represent IEL means; however, this was not explicitly stated.

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	table due to comparisons of interest made in the review. However we do not include these subjects in the sample size for this review.			poorer nutritional status had lower densities of mucosal TGF-β+ cells, with median densities of 420 and 250 cells/mm^2 in the grade I and grade II PEM groups, respectively. L:M values[10]: • Group 1: 0.53 (0.4-1.3) • Group 2: 0.47 (0.02-2.20) • Group 3: 0.73 (0.14-2.2) • Not assessed among the UK controls Nutritional status was not associated with L:M, recoveries of lactulose or mannitol. L:M was correlated with mucosal B lymphocyte density (r=0.57, p<0.05), IEL (r=0.51, p<0.02), and perforin+ IEL (r=-0.64, p<0.03).		
2002 Campbell DI et al. Age-related association of small intestinal mucosal enteropathy with nutritional status in	Keneba, The Gambia and surrounding villages 2-60 yr olds randomly selected from rural communities.	Cohort n=162; <5 yr old: n=26 (23 were re-assessed)	<u>Urine Tests</u>: • Lactulose[11] • Mannitol • L:M	Mean[12] L:M (SE) in 2-5 yr old group: 0.353 (0.022). Mean lactulose and mannitol % recovery was ~0.45 and ~0.65, respectively. L:M was highest in 2-5 yr age group and decreased with	Mean L:M in asymptomatic 2 to 5 yr olds was high and decreased significantly with increasing age, but never fell within expected range of values.	Subjects were free from diarrhea symptoms for at least one week prior to urinary assessments. The authors

[10] Not clearly indicated if these figures represent mean (CI) or another measure of central tendency.
[11] Lactulose and mannitol results were expressed as % of dose administered.
[12] Type of mean not specified.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
rural Gambian children L:M and urinary lactulose and mannitol recovery as a marker of intestinal permeability and its association with nutritional status at varying ages. Also assessed correlation of change in L:M with nutritional status at 3.5 mo re-visit.				increasing age (up to age 20) ($p<0.001$), but never fell within referenced UK normal ranges [201]. Most of the improvement in L:M was driven by a reduction in lactulose excretion ($p<0.001$), which fell within expected UK ranges by age 10 yr. In contrast, although mannitol excretion slightly decreased with age, this trend did not reach statistical significance. In fact, excretion proportions were at all times ½ - ⅓ of expected UK values [201]. L:M was inversely correlated with HAZ score[13] ($r=-0.31$, $p<0.001$), but not with WAZ or body mass index (BMI) Z scores. The correlation with HAZ score was mainly due to the higher lactulose excretion in subjects with poorer HAZ scores ($r=-0.22$, $p=0.001$) and held across all age groups. There was a small improvement in mean L:M (SE) between the two study time points from 0.198 (0.018) to 0.172 (0.010) ($p=0.026$ for change in L:M), driven by an improvement in mannitol recovery with no change in lactulose excretion.	Among all age groups, L:M showed significant intra-subject correlation between tests conducted 3.5 months apart. Among all age groups, L:M was significantly inversely correlated with HAZ score, primarily driven by lactulose excretion.	sought correlation between the mean L:M of the two visits and ΔBMIZ, ΔHAZ and ΔWAZ scores, but statistical calculations were not provided.

[13] Reported results were adjusted for age, sex, and visit.

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				Indices of intestinal permeability within subjects showed a high degree of correlation between the two visits:
				• Lactulose: r=0.55, p<0.001
				• Mannitol: r=0.24, p<0.05
				• L:M: r=0.66, p<0.001
				
				Change in measures between visits (analysis not stratified by age):
				• Mean L:M (SD):
				  • Visit 1: -1.62 (0.66)
				  • Visit 2: -1.76 (0.55), (p=0.026)
				• Mean mannitol recovery (SD):
				  • Visit 1: 5.25 (2.69)
				  • Visit 2: 6.28 (3.03), (p=0.006)
				• Mean lactulose recovery (SD):
				  • Visit 1: 0.28 (0.20)
				  • Visit 2: 0.29 (0.18), NS (p-value not specified)		

2003 Chen P et al. Association of vitamin A and zinc status with altered intestinal permeability: analyses of cohort data from northeastern Brazil	Goncalves Dias favela in Fortaleza, Brazil 2-97 mo olds recruited from an urban shantytown.	Cohort n=75 with pre-supplement L:M and retinol concentrations measured: • 51 with pre-supplement circulating	<u>Urine Tests</u>: • Lactulose[14] • Mannitol • L:M	Baseline mean (SD): • L:M[15]: 0.29 (0.16) • Lactulose: 0.54 (0.29) • Mannitol: 2.07 (0.88) L:M was not correlated with age. L:M was inversely correlated with retinol (r=-0.55, p<0.0005), including after adjustment for zinc	Supplementation of vitamin A and zinc resulted in significant improvements in L:M among the cohort of children with a history of PD or low WAZ score who received post-	Longitudinal data were not reported stratifying on underlying condition (i.e. PD history vs. WAZ score). Follow-up data

[14] For lactulose and mannitol results, excretion measurement was not specified.
[15] Type of mean not specified.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
L:M as a marker of intestinal permeability pre- and post-vitamin A and zinc supplementation among children with history of PD or low WAZ score		zinc concentrations measured • 20 with post-intervention* longitudinal follow-up of subset with history of PD or low WAZ score * These subjects received a single oral dose of vitamin A and a 2-wk course of daily zinc supplements.		concentration and stratification on retinol concentrations. Retinol was correlated with mannitol (r=0.28, p=0.017) and lactulose (r=-0.22, p<0.063) excretion. Lactulose, mannitol and their combined ratio were not correlated with zinc concentrations. L:M improved after supplementation for the cohort of 20 children followed longitudinally with PD or low WAZ score: L:M mean (SD): • Pre-treatment: 0.28 (0.12) • Post-treatment: 0.19 (0.07) However, lactulose and mannitol excretion did not change significantly.	supplementation assessment. Less than one-third of the subjects had post-intervention L:M assessments.	on L:M were not provided for the children with normal WAZ score or no history of PD. Unclear how long after supplementation the L:M testing was done. Post-supplementation L:M results in the text of the publication differed somewhat from what was reported in the publication table.
2002 Clark TD et al. Risk factors and cumulative incidence of anemia among human immunodeficiency virus-infected children in Uganda Association of chronic diarrhea with moderate anemia in HIV-infected children	Kampala, Uganda 9 mo old HIV-infected children followed at Mulago hospital until 36 mo of age. More than 40% were stunted and/or underweight at enrollment.	Cohort n=225	Blood Test: Hemoglobin	While chronic diarrhea was associated with moderate anemia in a univariate analysis (odds ratio=2.5, CI: 1.0, 6.3), it was either not associated with moderate anemia (hemoglobin <9 g/dL) in a multivariate model or not included in the model	While there was a high prevalence of anemia (<11 g/dL) and moderate anemia (<9 g/dL) (92% and 35% at 9 months, respectively) among this cohort of HIV-infected children, chronic diarrhea appears to have not been associated with anemia in the multivariate	The association between chronic diarrhea and other assessed hematologic markers (any degree of anemia, mean corpuscular volume, and mean corpuscular hemoglobin concentration) was not reported.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
					analysis. However, the text did not specifically state whether chronic diarrhea was tested in the multivariate model.	
2007 Darboe MK et al. Effectiveness of an early supplementation scheme of high-dose vitamin A versus standard WHO protocol in Gambian mothers and infants: a randomised controlled trial L:M as a marker of intestinal epithelial integrity among infants receiving high-dose vitamin A or standard vitamin A protocol	Keneba, The Gambia Subjects recruited at birth from rural community. Age range during study was 0-12 mo.	RCT n=197 n=99 received high dose vitamin A protocol n=98 received standard dose vitamin A protocol	<u>Urine Test</u>: L:M	Mean[16] L:M and proportion with values >0.30 among those receiving standard doses of vitamin A, by age: • 2 mo: 0.195, 12% • 5 mo: 0.197, 13% • 7 mo: 0.212, 22% • 9 mo: 0.286, 30% • 12 mo: 0.322, 34% Mean L:M differed between the two groups only at 7 mo (0.276 in high-dose vitamin A group, p=0.014), although there was no difference in percentages with L:M >0.30.	L:M values rose by ~50% from age 2 mo to 1 yr and were not affected by dosing of vitamin A.	The L:M normal cutoff was defined higher than for most other L:M studies, as 0.30. This was derived from the mean plus 2 SD from a study of UK infants [202]
2002 Dini E et al. Sudan III and steatocrit in the detection of fecal fat in malnourished children Fecal fat by four different testing methods as a marker	Caracas, Venezuela 6 mo-9 yr olds with recruited from an outpatient nutrition center and well-nourished controls.	Case-control n=129; n=99 cases: • 30 with subclinical malnutrition • 34 with mild malnutrition • 30 with moderate	<u>Stool Test</u>: Fecal fat, by method: • Sudan III classic • Sudan III modified • Steatocrit classic • Steatocrit acid Each subject underwent testing for	Proportions testing positive for fecal fat ranged from 33%-41% overall, depending on test method used. The proportion testing positive varied by nutritional status across testing methods: • 80%-100% of severely malnourished subjects had a positive test	A majority of children studied tested negative for fecal fat. The highest percent testing positive was in those with severe malnutrition, followed by those with subclinical-	Spanish language article. Control recruitment strategy was not well described. Proportions positive for fecal fat by history of diarrhea (current

[16] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
of malabsorption among children with varying nutritional status and well-nourished controls		malnutrition • 5 with severe malnutrition n=30 controls	all four methods.	• Similar proportions of subjects with subclinical, mild or moderate malnutrition tested positive, ranging from 30%-47% • 13%-27% of controls tested positive These differences appeared to be significant, but statistical comparison results were not entirely clear. Fecal fat did not vary based on quantity of fat intake. By all four methods, a high percentage of children with parasites tested positive (~60%) compared to children without parasites (25%). Associations were observed between infection with *Giardia lamblia* or *Blastocystis hominis* and fecal fat ($p<0.05$); this held true across diagnostic methods. The presence of diarrhea at time of testing was positively associated with fecal fat by all test methods ($p<0.02$ for all except steatocrit classic, $p=0.06$). The relationship between fecal fat and history of diarrhea in the year prior to testing varied by test method: • Sudan III classic: $p=0.134$	moderate malnutrition. Controls had the lowest percent testing positive. Subjects with enteric parasites or those experiencing diarrhea at time of testing excreted fat significantly more often than uninfected children without diarrhea, although the magnitude of difference was not reported. There was some variation between the different testing methods, for example their relationship with a history of diarrhea in the year prior to testing.	or previous) were not provided. Authors reported percent agreement between tests but did not report results of statistical testing of these estimates. Test results varied by subject characteristics; however, assessments adjusting for potential confounding were not reported.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				• Sudan III modified: p<0.001 • Steatocrit classic: p=0.14 • Steatocrit acid: p=0.015 Agreement between all four methods was 72%. Agreement between at least three was 91.5%.		

2006
 	
El Mouzan MI et al.
 	
Endoscopic duodenal biopsy in children
 	
Duodenal biopsy among children with suspected intestinal disease
	Riyadh, Saudi Arabia
	
	1.5 mo-18 yr olds referred to hospital for endoscopy with duodenal biopsy.
	
	78% of subjects were <12 yr old; results not presented by age.
		Retrospective case-series
		
		n=241 cases:
		• 102 with PD
		• 116 with unexplained short stature
		• 11 with refractory rickets
		• 12 with other conditions (including 2 with protein losing enteropathy)
			<u>Endoscopic duodenal biopsy:</u>
			• Gross endoscopic visualization
			• Histopathology
				14% had abnormalities on endoscopic visualization:
				• 1% had esophagitis
				• 6% had gastritis, 7 (47%) of which were *H. pylori* positive
				• 7% had duodenitis
				
				Biopsy results:
				• PD:
				  • 26% normal
				  • 29% chronic non-specific duodenitis
				  • 40% villous atrophy
				  • 5% other*
				
				• Short stature:
				  • 56% normal
				  • 22% chronic non-specific duodenitis
				  • 22% villous atrophy
				
				• Rickets:
				  • 55% normal
				  • 36% chronic non-specific duodenitis
				  • 9% villous atrophy
				
				• Other:
				  • 25% normal
				  • 50% chronic non-specific duodenitis
					Villous atrophy was identified not only among 40% of children with PD, but also among 22%, 9%, and 17% of those with short stature, rickets, and other conditions, respectively.
					
					Authors argue that endoscopic biopsy is superior to “blind” capsule biopsy in developing country settings and allows for visualization of the intestine.
					
					Endoscopic visualization results were not reported by condition nor in relation to histopathology results; it is difficult to assess the value added compared to biopsy alone.
						Specific results for the 2 patients with protein losing enteropathy were not reported.
						
						For 27% of cases, the only histopathology finding was chronic non-specific duodenitis; the diagnostic, prognostic, and therapeutic utility of identification is unclear.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				• 17% villous atrophy • 8% other* * 3 lymphangiectasia, 2 *Giardia*, 1 *Mycobacterium avium intracellulare.* Findings were reported according to presenting symptoms.		
2000 Fagundes-Neto U et al. Studies of the small bowel surface by scanning electron microscopy in infants with persistent diarrhea Scanning electron microscope (SEM) and light microscope (LM) analyses of small intestinal biopsy among infants with PD with and without SBBO	Sao Paulo, Brazil 2-10 mo olds with PD and protein calorie malnutrition consecutively admitted to Sao Paulo Hospital.	Case-series n=16	<u>Jejunal secretions aspirate:</u> Bacterial concentrations <u>Jejunal tethered capsule biopsy:</u> Histopathology by LM and SEM <u>Rectal tethered capsule biopsy:</u> Histopathology	68.7% had bacterial overgrowth (concentration $>10^4$ colonies/mL): 3 had enteropathogenic *E. coli* while the rest had colonic microflora. All small intestine specimens had morphological abnormalities on LM: • 43.7% moderate villous atrophy • 56.3% subtotal villous atrophy SEM revealed abnormalities of varying intensity: • Among the 11 with SBBO, villous atrophy ranged from Grade II (n=4), Grade III (n=2), to Grade IV (n=3). • For the 5 subjects without SBBO, villous atrophy ranged from Grade I (n=1) to Grade 2 (n=4). • A mucous-fibrinoid pseudo-membrane over enterocytes was noted in 7 of the 11 with SBBO and none of the others. Other abnormalities noted on SEM included:	Histological abnormalities were noted in all subjects by LM and SEM. Degree of villous atrophy noted on SEM seemed to be correlated with SBBO (no statistical tests were reported). Authors speculate that the mucous-fibrinoid pseudo-membrane partially covering enterocytes is consistent with a malabsorptive process, with the findings of fat droplets on enterocytes surfaces, and with the state of malnutrition of the subjects.	Inconsistent reporting of proportions of histopathologic findings among all subjects and by SBBO status; assessment of potential relationship with SBBO between different histologic findings was not possible.

Appendix 7. Evidence table of all studies included in the review.

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				• Mucus and debris covered large areas of the villous surface • Derangement of the enterocytes (in some cases cell borders were not clearly defined) • Reduced height and number (or absence in some places) of microvilli • Lymphocytes and fat droplets were observed over the surface of enterocytes (18%)[17] 10 subjects had colitis on rectal biopsy; this was not associated with SBBO or degree of small intestinal pathology on SEM.		

2001
 	
Filteau SM et al.
 	
The effect of antenatal vitamin A and (beta)-carotene supplementation on gut integrity of infants of HIV-infected South African women
 	
L:M as a marker of intestinal permeability among infants of HIV-infected mothers
	Durban, South Africa
	
	Pregnant, HIV-infected women between 28-32 wk gestation recruited from antenatal clinic. Infants were followed until 14 wk of age.
		RCT
		
		n=238
		
		n=119 received vitamin A supplements (26 with HIV infection)
		
		n=119 received placebo (29 with HIV infection)
			<u>Urine Tests</u>:
			• Lactulose[18]
			• Mannitol
			• L:M
			
			Subjects tested:
			• 1 wk:
			  • Treatment: n=104
			  • Placebo: n=104
			• 6 wk:
			  • Treatment: n=100
			  • Placebo: n=105
			• 14 wk:
			  • Treatment: n=99
				Mean L:M[19] (CI) at 1 wk among infants without reports of illness was 0.12 (0.08, 0.17). L:M did not change with increasing age and did not significantly increase with reported morbidity.
				
				While a history of ever having been breastfed was an important contributor to L:M at 1 wk (ΔR^2=0.22, p=0.008), a significant effect was not seen at 6 and 14 weeks[20]. Current feeding status had a modest effect on L:M only at
					Mean L:M overall was within normal range. However, mean L:M for placebo-treated, HIV-infected infants by 14 weeks was significantly elevated to almost 0.5.
					
					While HIV infection did not affect mannitol excretion, it was associated with increased
						Specific sugar excretion was normalized to urinary creatinine to control for variation in renal function.

[17] These SEM results were not presented separately for those with and without SBBO.
[18] For lactulose and mannitol results, excretion measurement was not specified.
[19] Geometric mean.
[20] Reported results were adjusted for confounding variables, unless otherwise noted.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments

enrolled in a vitamin A trial		Treatment involved maternal vitamin A supplements during pregnancy and at delivery.	• Placebo: n=95	14 wk (ΔR^2=0.06, p=0.04).
				
				Birth weight contributed significantly at 1 wk (ΔR^2=0.07, p=0.02), but current weight did not contribute significantly to L:M at any time point.
				
				HIV infection status by 14 wk was the major factor contributing to L:M at 6 wk (ΔR^2=0.22, p=0.008) and 14 wk (ΔR^2=0.21, p=0.01).
				
				Maternal HIV viral load during pregnancy was not consistently significantly correlated with infant L:M. Maternal lymphocyte counts and plasma retinol concentrations were not associated with infant L:M.
				
				While maternal vitamin A supplementation had no effect on L:M of uninfected infants, it appeared to prevent the increase in L:M of HIV-infected infants[21]:
				Mean[22] L:M (CI):
				• Uninfected:
				  • Vitamin A group: 0.11 (0.08, 0.15)
				  • Placebo group: 0.09 (0.06, 0.12)
				• HIV-infected:
					lactulose excretion.	

[21] Reported results were adjusted for confounding variables included an interaction with HIV infection.
[22] Geometric mean.

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				• Vitamin A group: 0.17 (0.13, 0.23) • Placebo group: 0.50 (0.37, 0.68) Mannitol was not affected by vitamin A. HIV infection was not consistently significantly associated with mannitol across age groups. Lactulose also did not consistently differ between treatment groups or by HIV-status, although vitamin A prevention of increase in lactulose among HIV-infected infants neared significance at 14 wk (p=0.058)[23].		

2005
 	
Galpin L et al.
 	
Effect of *Lactobacillus* GG on intestinal integrity in Malawian children at risk of tropical enteropathy
 	
L:M and sucrose: lactulose ratio (SUC:L) as markers of intestinal and gastric permeability, respectively, in asymptomatic children presumed at risk of
	Mwenye, Malawi
	
	36-60 mo olds recruited from a rural community, excluding children with severe acute malnutrition or severe chronic illnesses.
	
	Subjects were considered at risk for EED due to residence in a location with high prevalence of EED.
		RCT
		
		n=164;
		
		n=81 received *Lactobacillus* GG (80 completed the study)
		
		n=83 received placebo (81 completed the study)
		
		Subjects received 30-
			<u>Urine Tests</u>:
			• Lactulose[24]
			• Mannitol
			• Sucrose (SUC)
			• L:M
			• SUC:L
				At enrollment:
				• 73% had L:M >0.10
				• 40% had L:M >0.20
				• Mean[25] L:M (SD):
				  • Treatment: 0.18 (0.16)
				  • Placebo: 0.22 (0.20)
				• Mean lactulose (SD) in treatment group: 0.25 (0.17)
				• Mean mannitol (SD) in treatment group: 8.0 (4.5)
				• Mean SUC:L (SD):
				  • Treatment: 0.58 (0.64)
				  • Placebo: 0.60 (0.64)
				
				Mean excretion of sucrose (SD) increased from 0.057 (0.042) to 0.078 (0.058) in the treatment group (p=0.01), but
					A high baseline prevalence of abnormal L:M was observed, with no change after intervention.
					
					High mannitol excretion (relative to UK norms) drove the abnormal L:M.
					
					There was little effect on SUC:L with intervention; sucrose excretion increased in both treatment and
						Difficult to interpret sucrose tests because there are limited data on laboratory values for these tests in young children.

[23] P-values are from reported results that were adjusted for confounding variables.
[24] Lactulose, mannitol, and sucrose results were expressed as % of dose administered.
[25] Arithmetic mean.

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EED	Presumed that if SBBO is etiology for EED, treatment with *Lactobacillus* will result in improved gut integrity.	days of *Lactobacillus* GG or placebo. Only the 161 subjects who completed the study had repeat testing.		similar results were observed in the placebo group. Otherwise there were no changes in lactulose, mannitol, L:M, or SUC:L after treatment or placebo.	control groups.	
2001 Gandolfi L et al. Antiendomysial antibody test reliability in children with frequent diarrhea and malnutrition: is it celiac disease Jejunal biopsy among children with PD and/or malnutrition	Brasilia, Brazil 6 mo-13 yr olds with acute, persistent or chronic diarrhea, and/or malnutrition being seen at the pediatric gastroenterology service of a university hospital and determined to have disease severity warranting biopsy. Subjects negative for CD-specific antibodies were of interest for this review.	Cross-sectional n=31	<u>Jejunal capsule biopsy:</u> Histopathology	30/31 (96.8%) had abnormal histopathology: • Suggesting non-specific inflammatory abnormalities in 27 (87.1%) subjects. • Demonstrating grade 3 mucosal abnormalities in all malnourished 1 yr olds negative for enteric parasites.	The vast majority of children with clinically severe diarrhea and/or malnutrition had some degree of abnormality on jejunal biopsy.	Biopsies of interest were not provided in subject-specific detail (e.g. characteristics of the 27 children with non-specific inflammation were not detailed (e.g. presence of parasites, degree of malnutrition and/or diarrhea).
2008 R. Goto, et al. Impact of anti-*Giardia* and anthelminthic treatment on infant	Dhamrai Upazila, Bangladesh 3-15 mo olds from a rural area were enrolled and followed in a 9-mo	RCT n=222* n=75 received anti-*Giardia* and	<u>Urine Test</u>: L:M <u>Blood Tests</u>: • α-1-acid glycoprotein (AGP)	Mean L:M[26] (SD) at baseline was 0.18 (0.24) in treatment groups, with no significant difference in placebo group or in testing post-intervention. Proportion with elevated L:M	High L:M ratios overall with substantial seasonal and within-infant variability.	High L:M ratios were defined as greater than the upper CI for UK infants. Same study

[26] Geometric mean.

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growth and intestinal permeability in rural Bangladesh: a randomised double-blind controlled study L:M as a marker of intestinal permeability, IgG as a marker of chronic immune stimulation, and α-1-acid glycoprotein as an acute phase reactant among children undergoing anti-parasitic presumptive treatment vs. placebo. Also assessed markers' associations with growth parameters.	trial. There was a high prevalence of malnutrition in the study population.	anthelminthic treatment n=59 received anti-*Giardia* treatment only n=88 received placebo * Those who fully participated and for whom data were analyzed are included in this review.	• IgG • Albumin	at any study time point varied between 58%-74%. >57% consistently elevated L:M ratios. Seasonal variation in L:M was observed ($p < 0.001$), with highest mean values in the monsoon season. L:M was associated with ΔWAZ and ΔWHZ scores at 24 weeks ($p=0.001$ and $p<0.001$, respectively, point estimates not provided.) Serum immune marker values were similar in all groups and did not change substantially with interventions. AGP concentrations were negatively associated with ΔWAZ score at 24 weeks ($p=0.004$, point estimate not provided), and were associated with ΔWHZ score at 12 weeks but not at 24 weeks.	Interventions did not impact L:M or serum immune markers. There was improvement in weight with better L:M values, the degree to which this occurred was not reported.	population as reported by this group in another study also included in this review [123].
2008 Goto R et al. Impact of intestinal permeability, inflammation status and parasitic infections on infant	Dhamrai Upazila, Bangladesh 3-15 mo olds from a rural area were enrolled and followed in a 9-mo trial.	Longitudinal data extracted from an RCT [122] n=298 Urine and	<u>Urine Test</u>: L:M <u>Blood Tests</u>: • α-1-acid glycoprotein (AGP) • IgG • Albumin	Mean[27] L:M: 0.15 L:M showed a decreasing trend with age ($p=0.003$), and was associated with female gender ($p=0.004$), HAZ score ($p=0.039$), and WAZ score ($p=0.019$), but not with giardiasis or any of the serum	Mean L:M was elevated. L:M was not associated with any of the tested serum markers of inflammation or with giardiasis. IgG rose with	Helminthiasis prevalence was very low; testing for association with markers was not performed. Giardiasis was

[27] Geometric mean.

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growth faltering in rural Bangladesh L:M as a marker of intestinal permeability, IgG as a marker of chronic immune stimulation, and α-1-acid glycoprotein as an acute phase reactant. Also assessed laboratory values' associations with giardiasis and growth parameters.	There was a high prevalence of malnutrition in the study population.	blood samples were collected every 3 mo and anthropometric measurements were collected monthly.	• Hemoglobin	immune markers. IgG, AGP, and albumin were associated with giardiasis, but hemoglobin was not. Mean circulating albumin concentration was normal for age [203]. Compared to UK age-matched reference [199], rate of rise in IgG with increasing age was similar, but concentrations were consistently ~3g/L higher. IgG was not associated with growth parameters. Albumin was associated with HAZ score only (p=0.016). AGP was inversely associated with HAZ (p=0.011) and WAZ (p=0.005) scores.	increasing age at the rate expected (compared to UK norms) [199] but at higher concentrations across all ages.	defined as presence of a *Giardia*-specific IgM response. Same study population as reported by this group in another study also included in this review [122]. Cut-off values representing elevated concentrations have not been determined for AGP. UK norms for 10 mo olds-adults are 0.88 g/L mean (0.21 SD) [204].
2002 Goto R et al. Poor intestinal permeability in mildly stunted Nepali children: Associations with weaning practices and *Giardia lamblia* infection L:M as a marker of	Kathmandu, Nepal 0-5 yr olds (mean age 3.8 yr) from two urban squatter settlements. 37% and 33% of subjects were stunted and underweight,	Cross-sectional n=210	<u>Urine Tests</u>: • Lactulose[28] • Mannitol • Lactose[29] (168 tested) • L:M (158 tested) • Lactose:lactulose ratio (157 tested)	L:M: • 92% had values >UK norms • Mean[30] L:M (SD, range): 0.26 (0.21, 0.04-1.71). • *Giardia*-infected versus uninfected means: 0.43 vs. 0.25, p=0.014 The duration of ingestion of solid foods (with or without concurrent breastfeeding) was not associated with L:M in multivariate analysis.	L:M ratios were high overall. Wide individual variation was observed in L:M ratios. L:M was associated with giardiasis but not helminthiasis.	Low lactase activity was defined as lactose:lactulose ratio >0.4. Specific L:M data by WAZ and HAZ scores were not reported, although authors state

[28] Lactulose and mannitol results were expressed as % of dose administered.
[29] Lactose results were expressed in mg/L.
[30] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
intestinal permeability, and assessment of association with giardiasis, helminthiasis, nutritional practices, and growth status.	respectively.			L:M was correlated with longer duration of breastfeeding (r=0.27, p<0.019). Specifically, children who breastfed for >2 yr had higher L:M ratios than children who breastfed for shorter times (data not provided). L:M was not associated with: • History of diarrhea in the week preceding testing • Helminthiasis • Age • WAZ or HAZ scores Lactulose excretion ranged from 0.02–15.00. Mannitol excretion ranged from 0.5–15.00. 47% showed low lactase activity. Lactose values and lactose:lactulose ratios decreased with age (R^2=28%, p<0.0001), but were not associated with sex, ethnicity, and location nor were they associated with L:M. Mean[31] urinary lactose concentrations (mg/L) by feeding mode: • Breastfed: 172.5 • Non-breastfed: 44.5, p<0.0001 corrected for infant age	Urinary lactose concentrations and lactose:lactulose ratios were significantly higher in breastfed subjects than in those that were not breastfed, despite similar intestinal permeability values. There were some unexpected findings: the duration of breastfeeding, and not the timing of introduction of solid foods, was correlated with L:M, and the correlation was direct, not inverse. Authors speculate that this could be due to higher mean age of their cohort compared to another study that demonstrated beneficial effect of duration of breastfeeding on reduced L:M in Guatemala [205].	that L:M was not associated with "growth status."

[31] Geometric mean.

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Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				Mean[32] lactose:lactulose ratio by feeding mode: • Breastfed: 2.76 • Non-breastfed: 0.31, p<0.0001 corrected for infant age Mean L:M by feeding mode: • Breastfed: 0.23 • Non-breastfed: 0.28, non-significant, p-value not specified		

2000
 	
Haase A et al.
 	
Dual sugar permeability testing in diarrheal disease
 	
Lactulose:rhamnose ratio (L:R) as a marker of intestinal permeability in children with or without diarrhea. Also directly compared blood and urine methods of L:R testing in a subset of subjects.
	Darwin, Australia
	
	Cases were >4 mo olds admitted to Royal Darwin Hospital with diarrhea. Controls were patients admitted with non-GI illness.
	
	More than 75% of cases and controls were Aboriginal.
		Case-control
		
		n=264;
		
		n=150 cases with AD
		
		n=114 controls with no diarrhea
			<u>Blood Test</u>:
			L:R
			
			<u>Urine Test</u>:
			L:R
			
			Among cases:
			• 24 had both blood and urine L:R
			• 98 had blood L:R only
			• 28 had urine L:R only
			
			Among controls:
			• 25 had both blood and urine L:R
			• 36 had blood L:R only
			• 53 had urine L:R only
			
			A total of 49 subjects were tested with both blood and urine L:R methods to allow direct
				Among the subset with both blood and urine specimens:
				• Urine L:R:
				  • Mean[33] (CI):
				  • Cases: 12.4 (9.3, 16.5)
				  • Controls: 6.7 (5.0, 8.8), p=0.004
				  • Distribution across ratios:
				  • Low: n=31
				  • Intermediate: n=9
				  • High: n=9
				• Blood L:R:
				  • Mean[34] (CI):
				  • Cases: 9.4 (6.7, 13.1)
				  • Controls: 5.9 (4.4, 7.8), p=0.04
				  • Distribution across ratios:
				  • Low: n=27
				  • Intermediate: n=11
				  • High: n=11
					Children with diarrhea had significantly higher L:R ratios by both blood and urine testing compared with controls without GI illness.
					
					There was substantial agreement between urine and blood L:R tests in the same subjects.
					
					Urine has been an established substrate for sugar excretion assessment as an indication of intestinal permeability.
						Authors used data from non-diarrheal controls from their clinical practice to derive cut-points for L:R ratios used in this study:
						• Blood L:R:
						  • Low= <7
						  • Intermediate= 7-12.5
						  • High= >12.5
						• Urinary L:R:
						  • Low= <10
						  • Intermediate= 10-18
						  • High= >18
						
						Controls were significantly

[32] Geometric mean.
[33] Geometric mean.
[34] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

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			comparison of values.	Among subjects with only urine tested: Mean[35] urine L:R (CI): • Cases: 15.7 (12.6, 19.6) • Controls: 6.7 (5.7, 8.0), p<0.0001 Among subjects with only blood tested: Mean[36] blood L:R (CI): • Cases: 12.8 (10.3, 16.0) • Controls: 3.7 (2.8, 4.9), p<0.0001 Even though blood L:R was consistently lower than urine L:R by a geometric mean (CI) of 1.09 (1.02, 1.16), there was strong correlation between L:R ratios in blood and urine as measured by: • Concordance correlation coefficient for agreement (CI) of 0.76 (0.64, 0.88) • Kappa statistic (CI) of 0.71 (0.51, 0.92) (when L:R ratios are divided into 3 ordered categories) • Sensitivity and specificity of blood tests of 81% (25/31) and 89% (16/18), respectively, when using the urine testing as the standard. The failure rate* for serum	However, timed collection of urine is not a trivial task, especially among female children, and contamination with stool is problematic, especially in children with diarrhea. However, the much lower concentrations of probe sugars in blood compared to urine had posed a challenge to sensitive detection in blood. High performance liquid chromatography (HPLC) methods, as used in this study, now provide a more sensitive method of assessing blood specimens. The failure rate of L:R blood testing was significantly lower than that of urine testing.	older than the cases, but authors suggest that age differences do not impact L:R test performance. Numbers of subjects do not always match up (e.g. numerator in test failure rate calculations does not match other such reported numbers). Analyses of those subjects who had both blood and urine testing were conducted on combined cases and controls. Analyses of those with and without diarrhea would have been of interest. One would expect children with diarrhea to have higher rates of urine

[35] Geometric mean.
[36] Geometric mean.

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				L:R testing (20/197, 10%) was lower than for urine testing (86/234, 37%) (p<0.0001). * Defined as emesis with rhamnose/lactulose oral challenge (same dose for urine and serum testing), urine leakage or contamination with stool, or plasma quantity from blood draw of insufficient quantity for analysis.		test failure due to contamination with stool and to have higher failure rates using either analytes due to higher rates of emesis. Spot blood testing might be more feasible than timed urine collections, but HPLC might not be feasible in resource-poor settings. This study appears to report on the same population as two other studies in this review which also assessed serum L:R as a marker of intestinal permeability [43, 58].
2000 Hafeez A et al. An audit of pediatric upper gastrointestinal endoscopies	Islamabad, Pakistan 2 mo-12 yr olds referred from various hospitals to KRL Hospital Islamabad for	Case-series n=41; • 28 with PD • 9 with FTT • 4 with short stature	<u>Endoscopic duodenal Biopsy:</u> • Gross endoscopic visualization • Histopathology	Positive histopathologic findings were identified in: • 21/28 with PD • 7/9 with FTT • 3/4 with short stature More abnormalities were found via histology than	75% of the PD and 77% and the short stature/FTT patients had abnormalities by endoscopy. Authors assert the	There was possible bias in the manner of selection for endoscopy. 14 biopsies were unable to be analyzed (from

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Duodenal biopsy among children with PD or growth problems	abdominal pain, PD, short stature, FTT, GI bleeding, or anemia. The subjects of interest for this review were those with PD or growth problems.			visualization, and findings did not necessarily correlate.	importance of biopsies among children with indications for endoscopy, due to lack of correlation between them and increased identification of abnormalities by biopsy.	100 endoscopies). Authors did not report the endoscopic appearance of the mucosa. Histology findings were reported by specimen (with multiple specimens from some patients), not by condition or by patient, so specific results could not be interpreted in regards to this review.

Appendix 7. Evidence table of all studies included in the review.

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2007 Jain S et al. Fecal occult blood screening in children with severe malnutrition Fecal occult blood among severely malnourished children compared to healthy controls	Delhi, India Children (ages unspecified) admitted with severe malnutrition and age-matched healthy controls recruited from an immunization clinic.	Case-control n=80; n=50 cases with severe malnutrition n=30 healthy controls	Stool Test: Occult blood Blood Test: Hemoglobin	Fecal occult blood test was positive in 30/50 (60%) cases and 0/30 controls. Among cases positive for fecal occult blood, 20 (66.7%) were found to have hemoglobin <8 g/dL. Enteric infections: • Parasitic infections were detected in 14/50 (28%) of cases, 12 (85.7%) of whom tested positive for fecal occult blood. • Bacterial infections were detected in 18/50 (36%) of cases, 13 (72.2%) of whom tested positive for fecal occult blood. • Of the remaining 18 for whom an enteric pathogen was not identified, 5 (27.8%) tested positive for fecal blood. Among the 30 cases with fecal occult blood, 16 were breastfed, 11 were fed cow's milk, and 3 were fed formula.	A high proportion of severely malnourished children had a positive fecal occult blood test, compared with no positives among healthy controls. Malnourished children with identifiable pathogens more often tested positive for fecal occult blood, although approximately 25% of those without an identifiable pathogen also tested positive. Presence of fecal blood did not appear to vary by feeding mode (e.g. breast milk, cow's milk, or formula), although data presented were limited.	Among cases, half had a presenting complaint of diarrhea (duration not specified), but the authors did not report results stratified by diarrhea duration. Authors did not provide differences in proportions of occult blood among those with and without specific enteric pathogens. Statistical analysis was not provided; data were reported as proportions only. Matching scheme was not defined.

Appendix 7. Evidence table of all studies included in the review.

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2002 Kapoor S et al. Detecting protein losing enteropathy by Tc-99m dextran scintigraphy: A novel experience Tc-99m dextran scintigraphy as a marker of protein-losing enteropathy or intestinal inflammation	New Delhi, India 2-12 yr olds selected from hospitalized patients with symptoms suspicious for protein-losing enteropathy (hypoalbuminemia and edema).	Case-series n=3 <5 yr old	Tc-99m dextran scintigraphy	Abnormal Tc-99m dextran uptake was positive in one child found to have subtotal villous atrophy on biopsy and another thought to have abdominal tuberculosis. The child with the negative scan had marasmus and partial villous atrophy on biopsy.	Scintigraphy might be a useful, noninvasive method for detecting intestinal pathology.	This pilot study had a small sample size of 8 children, and only 3 were younger than 5 years.
2001 Kapoor S et al. Giardiasis--clinical and diagnostic perspective Immunoglobulin concentrations in duodenal fluid and serum among children with PD and *Giardia* infection compared to those without diarrhea	New Delhi, India <12 yr olds admitted to hospital with PD and *Giardia*. Controls had no diarrhea and were hospitalized for non-GI conditions. Most cases were <7 yr old, with n=19 <3 yr old. Ages of controls were not specified.	Case-control n=40; n=30 cases with PD and *Giardia* n=10 controls without diarrhea	<u>Duodenal secretion aspirates</u>: • IgG • IgM • IgA <u>Blood Tests</u>: • IgG • IgM • IgA	Higher mean concentrations of IgM were found in duodenal aspirates of cases compared to controls ($p<0.05$). Mean concentrations of duodenal IgA and IgG did not differ between cases and controls.	Differences in immunoglobulin concentrations were limited among children with PD infected with *Giardia* compared to children without such conditions.	The number of controls was small due to constraints in obtaining duodenal aspirate from children without GI symptoms.
2006 Kirkpatrick BD et al. Serum mannose-binding lectin deficiency is associated with	Port-au-Prince, Haiti <36 mo old inner-city residents recruited from the rehydration unit at the State	Case-control n=99; n=49 cases with *Cryptosporidium* infection (22 with PD)	<u>Blood Test</u>: Mannose-binding lectin (MBL)	Serum MBL concentrations were lower in cases than in healthy controls ($p=0.002$) and diarrhea controls ($p=0.045$). Percentage MBL-deficient: • 36.7% cases	While cryptosporidiosis was associated with MBL deficiency, MBL concentrations were not significantly	MBL deficiency was defined as concentrations <u>≤</u>70 ng/mL.

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cryptosporidiosis in young Haitian children Mannose-binding lectin as a marker of innate immune response among children with and without *Cryptosporidium* infection	University Hospital or from GHESKIO HIV Center[37]. All subjects were HIV-negative.	n=9 diarrhea controls negative for *Cryptosporidium* n=41 healthy controls without diarrhea and *Cryptosporidium*-negative		• 9.8% healthy controls • 0 diarrhea controls Cryptosporidiosis was associated with MBL deficiency (odds ratio=22.4; CI: 3.1, 160.8[38]). Among cases, the proportion of those with PD was nearly double among those with MBL deficiency compared to those without MBL deficiency, but these results were not significant (p=0.13). MBL deficiency was not associated with duration of diarrhea (p=0.37) among those with cryptosporidiosis nor with anthropometric status among either cases or controls.	associated with mean duration of diarrhea or history of PD.	

2006
 	
Kirkpatrick BD et al.
 	
Childhood cryptosporidiosis is associated with a persistent systemic inflammatory response
 	
Fecal cytokines and lactoferrin as markers of intestinal
	Port-au-Prince, Haiti
	
	<36 month olds recruited from GHESKIO HIV Center[39] with *Cryptosporidium* infection and healthy controls.
	
	Subjects were followed-up at 6 and 9 months after
		Cohort
		
		n=73;
		
		n=42 cases with diarrhea and *Cryptosporidium* infection (18 with PD)
		
		n=31 healthy controls without diarrhea and *Cryptosporidium*-
			<u>Stool Tests</u>:
			• Lactoferrin
			• Cytokines:
			  • IFN-γ
			  • TNF-α
			  • TGF-β
			  • IL-4
			  • IL-8
			  • IL-10
				Proportion lactoferrin-positive at enrollment:
				• Cases: 51.2%
				• Controls: 4.0%
				
				Cases had higher concentrations of TNF-α than controls at enrollment (p=0.04), but no difference was observed at follow-up.
				
				Controls had almost 2x higher fecal IFN-γ at enrollment (p=0.1); the
					Lactoferrin was present among half of subjects with cryptosporidiosis and uncommon among those without such infection.
					
					Fecal TNF-α was higher among cases at enrollment but did
						Cut-off values for lactoferrin positivity were not provided.
						
						Breastfed children (>85% of cases and controls) were included in testing. Proportions at follow-up were not reported.
						
						The association of fecal cytokines and

[37] The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections.
[38] Reported results were adjusted for confounding variables, unless otherwise noted.
[39] The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections.

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mucosal inflammation among children with and without *Cryptosporidium* infection	infection resolved. HIV status of subjects varied. There was a high prevalence of malnutrition in the study population.	negative		magnitude of difference increased (to almost 3x) and was statistically significant at the 6- and 9-month follow-up (p=0.01 and p=0.03, respectively). No differences in fecal concentrations of TGF-β, IL-8, IL-4, or IL-10 were noted between groups.	not persist when infection resolved. Paradoxically, controls' comparatively higher fecal IFN-γ increased in both magnitude and degree of statistical significance at follow-up. Of the remaining fecal cytokines assessed, there were no differences between cases and controls.	lactoferrin with growth parameters, history of PD, and HIV status were not reported, nor was their association with each other. Various markers of systemic inflammation, including serum cytokines, were measured but their relationship with markers of intestinal inflammation was not reported.

2002
 	
Kirkpatrick BD et al.
 	
Cryptosporidiosis stimulates an inflammatory intestinal response in malnourished Haitian children
 	
Stool lactoferrin, reducing substances, leukocytes and cytokines as markers of intestinal inflammation of
	Port-au-Prince, Haiti
	
	<18 mo olds from a low SES setting recruited from the rehydration unit of GHESKIO HIV Center[40] with diarrhea and *Cryptosporidium* infection. Controls recruited from an outpatient clinic without *Cryptosporidium* infection included those with and
		Case-control
		
		n=49;
		
		n=17 cases with *Cryptosporidium* and diarrhea (5 with PD)
		
		n=32 controls without *Cryptosporidium*;
		• 17 with diarrhea (5 with PD)
		• 15 healthy
			<u>Stool Tests</u>:
			• Reducing substances (RS)
			• Lactoferrin
			• Cytokines:
			  • TNF-α receptor I
			  • IL-4
			  • IL-8
			  • IL-10
			  • IL-13
			  • IFN- γ
			
			<u>Blood Test</u>:
			WBC
				Proportion RS-positive:
				• 33.3% cases
				• 64.7% diarrhea controls
				• 46.7% healthy controls, (p=0.2)
				
				Proportion lactoferrin-positive:
				• 83.3% cases
				• 60.0% diarrhea controls
				• 28.6% healthy controls, (p=0.01)
				
				IFN-γ was not recovered in any stools.
				
				All other fecal cytokines were significantly
					Fecal lactoferrin was identified most often in children with diarrhea, especially in those with *Cryptosporidium.* While some fecal cytokines were detected in as many as 40% of healthy controls and 70% of controls with diarrhea, they were generally associated with	Reported results were not stratified by persistent vs. acute diarrhea status.
						
						Cut-off values for lactoferrin positivity were not described.
						
						Stools from children who were breastfeeding were not tested for lactoferrin.

[40] The Haitian Group for the Study of Kaposi's Sarcoma and Opportunistic Infections.

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Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
children with and without *Cryptosporidium infection*	without diarrhea.			associated with *Cryptosporidium* cases compared to diarrhea and healthy controls. Additionally, TNF-α receptor I, IL-8, and IL-13 were found in diarrhea and healthy controls, while IL-4 and IL-10 were not. Fecal lactoferrin was associated with the presence of TNF-α receptor I (point estimate not provided, p=0.03). Mean WBC counts were within normal range in all 3 groups.	*Cryptosporidium* infection. The other stool tests did not discriminate by diarrhea or *Cryptosporidium* status.	
2008 Kohli A et al. *Giardia duodenalis* assemblage, clinical presentation and markers of intestinal inflammation in Brazilian children Fecal lactoferrin as a marker of intestinal inflammation in *Giardia*-infected children and its association with persistence of diarrhea	Goncalves Dias favela in Fortaleza, Brazil All newborns from an urban shantytown were recruited at birth and followed for up to 4 yr. Those with *Giardia* recovered from stools were included in this study.	Cohort n=108 stool samples from 47 children Stools were collected at regular intervals as well as during episodes of diarrhea.	Stool Test: Lactoferrin	Proportion of positive lactoferrin results decreased with each new *Giardia* infection, p=0.015: • 1st infection: 74.0% (15.2% of those testing positive had high titers) • 2nd infection: 40.0% (5.3% of those testing positive had high titers) • 3rd infection: 1 (20.0%) tested positive (at a high titers) Increasing titers of lactoferrin were associated with longer duration of diarrhea, p=0.017: • Negative: 2.2 days • Low: 9.7 days • High: 14.6 days	Increased concentrations of lactoferrin were observed more frequently with first time *Giardia* infections. Concentrations were associated with longer duration of diarrhea, although these results were not presented separately for first and recurrent infections. Stool lactoferrin might be useful in predicting	Lactoferrin results were graded based on agglutination reaction positivity with increasing dilution; the following scale was used: • High = positive at 1:400-1:3200 dilution • Low = positive at 1:25-1:200 • Negative = no reaction at 1:25 Stools from children who were breastfeeding were not tested.

Appendix 7. Evidence table of all studies included in the review.

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				Lactoferrin results did not differ between symptomatic and asymptomatic children at first infection, but those with symptoms had positive results with recurrent infections with greater frequency (75.0% vs. 0 in asymptomatic repeat infections, p=0.017.)	duration of diarrheal illness in *G. duodenalis*-infected children.	Data were part of a larger study; similar data on lactoferrin in *Cryptosporidium*-infected children were published by O.Y. Bushen, et al. (also included in this review); however, Bushen et al. used a slightly different grading scale for reporting lactoferrin results [108].
2003 Kukuruzovic RH et al. Increased nitric oxide production in acute diarrhea is associated with abnormal gut permeability, hypokalemia and malnutrition in tropical Australian aboriginal children Nitric oxide (NO) as a marker of intestinal permeability and inflammation, and lactulose:rhamnose ratio (L:R) as a marker of intestinal permeability and the relationship	Darwin, Australia 1-6 yr old Aboriginal and non-Aboriginal hospital inpatients. Subjects were grouped as follows: 1. Children with AD 2. Children with no diarrhea but with non-GI infectious conditions 3. Children without GI or infectious conditions	Case-control n=318; n=169 cases with AD (154 Aboriginal) n=149 controls: • 73 with non-GI infections (49 Aboriginal) • 76 with no infections (29 Aboriginal)	<u>Urine Test</u>: Nitric Oxide (NO)* <u>Blood Tests</u>: L:R Mean corpuscular volume (MCV) <u>Stool Test:</u> Reducing substances (RS)** (169 cases tested) * NO is an unstable free radical and is converted to nitrite and nitrate. Urine nitrate (NO_3)+ nitrite (NO_2) was expressed as a ratio with urine creatinine (NO_2 + NO_3:Cr) in order to account for	NO among Aboriginal children with diarrhea was >3x higher than any other group and >5x higher than in non-Aboriginal controls. • NO was >3x and >2x higher among Aboriginal than non-Aboriginal children in the diarrhea (p<0.001) and no infections groups (p<0.001), respectively, but there was no difference between them in the non-GI infections group. • NO was >3x and ~2x higher in the diarrhea compared to the no infections group among Aboriginals (p<0.001) and non-Aboriginals (p<0.03), respectively. • NO was virtually the same among the Aboriginal non-GI infections and no	NO_2 + NO_3:Cr ratio, as a measure of endogenous nitric oxide production, was used as a marker of gut permeability and inflammation, with an attempt to identify how much more it reflects as response to inflammation from GI vs. non-GI infections. Among non-Aboriginal controls, NO production was the same among those with diarrhea and non-GI infections (and higher compared	Positive stool RS was defined as <u>≥</u>0.5%. Abnormal L:R was defined as >7.6; no reference or derivation was provided for this cut-point. Study population appears to be the same as in another Kukuruzovic, et al. study also included in this review which assessed serum lactulose:rhamnose as a marker of intestinal permeability [58].

Appendix 7. Evidence table of all studies included in the review.

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between NO and L:R, growth parameters, mean corpuscular volume (as a surrogate of iron deficiency), and stool reducing substances among children with and without diarrhea			differences in urine concentration. ** Measured only among children with profuse diarrhea.	infections groups, as well as among the non-Aboriginal diarrhea and non-GI infections groups. 112/152 (74%) and 31/169 (18%) of children with AD had abnormal L:R ratios and positive stool RS, respectively. NO and L:R were measured at "convalescence" on Day 5 among those with diarrhea: the mean improvement in NO was 21.7% compared with 54.6% for L:R (p=0.01). NO and L:R were correlated (n=193, r=0.37, p<0.001)[41]; the correlation was stronger for lactulose (effect ratio=1.47, p<0.001) than for rhamnose (effect ratio=0.80, p=0.02[42]). NO was not correlated with stool RS[43] or MCV, but was correlated with lower WAZ score (effect ratio=0.88, p=0.05).	to controls). NO was highest by far among Aboriginal children with diarrhea compared to any other group. Authors suggest that high basal concentrations of NO among Aboriginal children due to (clinically silent) enteropathy could explain the concentrations seen among Aboriginal controls in this study. NO appeared to decrease significantly more slowly than L:R among children recovering from diarrhea. NO was found to correlate with L:R. NO was more strongly correlated with lactulose than rhamnose.	

[41] Reported results appear to have been adjusted for age and race.
[42] Reported results were adjusted for age and race.
[43] Reported results among children with diarrhea were adjusted for age and race.

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2002 Kukuruzovic RH et al. Milk formulas in acute gastroenteritis and malnutrition: a randomized trial Lactulose:rhamnose ratio (L:R) as a marker of intestinal permeability among children with diarrhea and/or malnutrition treated with milk formulas of varying composition and osmolality	Darwin, Australia Inpatient Aboriginal children <3 yr old with AD and/or WAZ score <-2. 60% of subjects had low WAZ score and 90% had diarrhea.	RCT n=177; n=60 received De-Lact formula n=65 received O-Lac formula n=52 received Alfaré formula Subjects were treated with one of three low-lactose formulas: • De-Lact, low-osmolality lactose-free formula • O-Lac, lactose-free formula • Alfaré, partially hydrolyzed formula	<u>Blood Test</u>: L:R L:R testing was repeated in 150 subjects at day 5: • De-Lact: n=48 • O-Lac: n=52 • Alfaré: n=50	Baseline mean[44] L:R (CI) in De-Lact group was 14.9 (10.4, 21.5), with no difference between groups. The mean improvement* in L:R (CI) was 13.0 (9.3, 16.6) with some significant differences between the various formulas: • De-Lact: 18.6 (10.6, 26.6) • O-Lac: 12.0 (7.5, 16.6), p=0.15 compared to De-Lact • Alfaré: 8.5 (2.1, 14.9), p=0.049 compared to De-Lact * Improvement in L:R was calculated as baseline L:R minus repeat L:R.	Authors noted that treatment with all of the low-lactose formulas studied resulted in improved L:R among this population at risk for enteropathy and growth failure. Improvement was most marked with the low osmolality formula, De-Lact.	Reported results did not appear to be harmonized with the method described for calculating improvement in L:R. Fully breastfed children were excluded. The study did not include a control arm (of standard care) to which change in L:R could be compared. Authors reiterate the advantages of serum over timed urine collection for assessment of L:R as discussed in another publication in this review [125].

[44] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
2002 Kukuruzovic RH et al. Small bowel intestinal permeability in Australian Aboriginal children Serum lactulose: rhamnose ratio (L:R), serum lactose, and stool reducing substances as markers of intestinal permeability among Aboriginal and non-Aboriginal children with and without diarrhea	Darwin, Australia Cases were Aboriginal and non-Aboriginal children admitted to hospital with diarrhea. Controls were Aboriginal and non-Aboriginal children admitted without GI illnesses.	Case-control n=375 admissions for 306 children; n=285 case admissions for AD (264 Aboriginal) n=90 control admissions with no diarrhea (74 Aboriginal)	<u>Blood Tests</u>: • Lactose • Lactulose[45] • Rhamnose • L:R • Hemoglobin • Mean corpuscular volume (MCV) <u>Stool Test</u>: Reducing substances (RS)* L:R testing was repeated on day 5 for a subset of Aboriginal subjects: • 174/264 admissions for acute diarrhea • 25/74 control admissions * Measured only among children with profuse diarrhea when "clinically indicated." Number tested not provided.	27/75 (36%) of Aboriginal controls and 0 non-Aboriginal controls had abnormal L:R ratios. Mean[46] L:R at baseline: Cases: • Aboriginal: 16.4 • Non-Aboriginal: 7.9, p=0.002 compared to Aboriginal cases Controls: • Aboriginal: 4.6 • Non-Aboriginal: 2.5, p=0.02 compared to Aboriginal controls Mean improvement[47] in L:R (CI) at day 5 among those with repeat testing: • Aboriginal cases: 14.6 (11.2, 18.0) • Aboriginal controls: -0.63 (-4.0, 2.7) Mean lactulose recovery[48]: • Cases day 1: 0.085 (0.070–0.103) • Cases day 5: 0.039 (0.033–0.046) • Controls: 0.024 (0.019–0.029) All 3 values significantly differed from one another. Mean rhamnose recovery:	Mean L:R ratios of Aboriginal children were approximately double those of non-Aboriginal children both among those with and without diarrhea, consistent with authors' suggestion that clinically silent enteropathy is prevalent among Aboriginal children. Mean L:R significantly improved over 5 days among Aboriginal cases. Children with severe diarrhea had higher mean L:R. Higher case L:R was driven more by high lactulose than by low rhamnose. Similarly, improvement in	Positive stool RS was defined as ≥0.5%. Abnormal L:R was defined as >5.6, derived from 2 SD above the arithmetic mean for non-Aboriginal controls in this study. The rationale for the choice of 2 SD above the arithmetic, instead of the geometric, mean is not clear. Proportions of cases with abnormal concentrations were not reported. Analysis included data for 69 children with repeat admissions; this might violate independence assumptions for their statistical analysis methods. Repeat L:R testing was conducted on

[45] Lactulose and rhamnose results were expressed as % of dose administered.
[46] Geometric mean.
[47] Improvement in L:R appears to have been calculated as baseline L:R minus repeat L:R, as described in another publication in this review; however, this was not expressly stated. Reference 134. Kukuruzovic, R.H. and D.R. Brewster, *Milk formulas in acute gastroenteritis and malnutrition: a randomized trial.* J Paediatr Child Health, 2002. **38**(6): p. 571-577.
[48] Figures reported parenthetically after the mean percent recoveries of lactulose and rhamnose were not specified as ranges or CIs.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				• Cases day 1: 0.479 (0.424–0.542) • Cases day 5: 0.555 (0.498–0.616) • Controls: 0.585 (0.500–0.685) These values did not significantly differ from one another. Confidence intervals (CIs) in the authors' graphical representation of mean L:R at admission did not overlap, and the difference in means was particularly evident between Aboriginal and non-Aboriginal subjects. Factors associated with L:R among cases were[49]: • Acidosis (p=0.007) • Hypokalemia (p=0.035) • Diarrhea severity (p=0.001) Age and malnutrition were not associated with L:R. 38% and 27% of Aboriginal cases had positive serum lactose and stool RS, respectively. 12% of Aboriginal and non-Aboriginal controls combined had lactosemia. Presence of lactosemia was associated with L:R,	L:R among cases was primarily due to decreased lactulose. Stool RS and serum lactose were found in approximately one-quarter and one-third of Aboriginal cases, respectively. The latter was weakly associated with increased lactulose.	controls of both racial groups, but among cases it was only conducted on Aboriginal cases. This study appears to report on the same population as in the Kukuruzovic, et al. 2003 reference also included in this review, which assessed nitric oxide excretion [43]. Authors reiterate the advantages of serum over timed urine collection for assessment of L:R, as discussed in another publication in this review [125].

[49] Reported results were adjusted for confounding variables, unless otherwise noted.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				adjusted relative risk (CI)=1.06 (1.03, 1.10)[50]. Stool RS, anemia, and MCV were not associated with L:R.		

[50] Reported results were adjusted for severity of diarrhea, acidosis, hypokalemia, and age.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
2004 Laadhar L et al. Determination of anti-transglutaminase antibodies in the diagnosis of celiac disease in children: results of a five year prospective study Duodenal biopsy among patients with suspected CD	Sfax, Tunisia Children admitted for endoscopic biopsy for symptoms of CD (not specified). Subjects of interest for this review were those who tested negative for CD-specific serology and who did not meet the study diagnostic criteria for CD--subtotal or total villous atrophy consistent with Marsh stages 3 or 4. Controls were aged 3 mo-17 yr (mean 4.5 yr).	Case-control n=99	<u>Endoscopic duodenal biopsy:</u> Histopathology	Of 99 subjects not meeting diagnostic criteria for CD, endoscopic biopsies revealed: • 76 had normal morphology of the intestinal mucosa • 7 had elevated densities of intraepithelial lymphocytes • 10 had partial villous atrophy (Marsh stage 2) • 6 had various other conditions such as giardiasis or gastritis	Among 169 children with symptoms of CD, 41% had subtotal or total villous atrophy, 10% had partial villous atrophy or inflammatory findings, and 45% had normal biopsies.	Article in French. Prevalence of CD antibodies did not clearly align with case/control designation. Because of the way the results were reported, we could not extract data on those who tested negative for CD-specific serology and who had Marsh stages 3 or 4 histopathology. Methods section described obtaining duodenal biopsies, while results and conclusion sections specify that jejunal specimens were obtained.

Appendix 7. Evidence table of all studies included in the review.

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2006
 	
Leite CA et al.
 	
Functional, microbiological and morphological intestinal findings among human immunodeficiency virus infected children
 	
Small intestinal and rectal biopsy to assess morphology and D-xylose as a marker of malabsorption among HIV-infected children
	Sao Paulo, Brazil
	
	5 mo-12 yr old (median 24 mo) HIV-infected subjects recruited from a hospital and clinic.
	
	All subjects had some degree of protein-energy malnutrition.
		Cohort
		
		n=11;
		
		n=5 patients with current or recent episode of diarrhea
		
		n=6 patients with no diarrhea in the 30 days preceding enrollment
			<u>Blood Test</u>:
			D-xylose
			(9 tested)
			
			<u>Biopsy of small intestine by tethered capsule or endoscopy:</u>
			Histopathology
			(10 tested)
			
			<u>Rectal biopsy</u>:
			Histopathology
			(6 tested)
				100% had low D-xylose absorption:
				• Mean: 15.6 mg/dL
				• SD: 5
				• Range: 8.9-24.4
				• Median: 14.2
				
				Small intestinal biopsy:
				• 100% had some degree of villous atrophy based on a I-IV grading system:
				  • Grade I: 3
				  • Grade I/II: 2
				  • Grade II: 1
				  • Grade II/III: 1
				  • Grade III/IV: 1
				  • 2 samples were too superficial to assess
				• Intraepithelial lymphocytes were increased in half of the biopsies.
				• Lymphocytic and polymorphonuclear (PMN) infiltration of the lamina propria were present in 10/10 and 7/10 biopsies, respectively.
				
				Rectal biopsy:
				• 100% had normal architecture
				• Lymphocytic and PMN infiltration were present in 6/6 and 4/6, respectively.
					There was a high prevalence (100%) of abnormal D-xylose results among HIV-infected children, regardless of diarrhea status.
					
					All patients also had cellular infiltration of the lamina propria and varying degrees of villous atrophy.
					
					There was no correlation between D-xylose and degree of villous atrophy on biopsy.
						Portuguese language article.
						
						D-xylose <25 mg/dL was defined as indicative of malabsorption. This value is higher than what some references have noted as a cut-point [186].
						
						Investigators used a well-articulated system of grading villous atrophy.
						
						Results were not presented by diarrhea status, perhaps due to small sample size.

Appendix 7. Evidence table of all studies included in the review.

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2010
 	
Lima AA et al.
 	
Effects of vitamin A supplementation on intestinal barrier function, growth, total parasitic, and specific *Giardia* spp infections in Brazilian children: a prospective randomized, double-blind, placebo-controlled trial
 	
L:M as a marker of intestinal barrier function, and stool lactoferrin and specific intestinal immunological cytokines as markers of intestinal inflammation among nutritionally at-risk children who received either vitamin A or placebo
	Fortaleza, Brazil
	
	2 mo-9 yr olds (mean 43 mo) from an impoverished urban community, eligible if HAZ score was <median for their community.
	
	Subjects were screened for intestinal parasites, and longitudinal anthropometrics were assessed.
		RCT
		
		n=79;
		
		n=40 received placebo (tocopherol)
		
		n=39 received vitamin A (retinyl palmitate)
		
		Subjects were treated every 4 mo.
			<u>Urine Tests</u>:
			• Lactulose[51]
			• Mannitol
			• L:M
			
			<u>Stool Tests</u>:
			• Lactoferrin
			• Cytokines:
			  • IFN-γ
			  • TNF-α
			  • IL-4
			  • IL-10
				Median L:M at baseline was 0.089. There was no significant change in L:M at 4 mo follow-up within either treatment group.
				
				No significant difference in L:M was observed between treatment groups.
				
				Both median lactulose and mannitol excretions decreased at 4 mo follow-up among the vitamin A compared to the placebo group:
				• Lactulose: 0.21 to 0.74, p=0.042
				• Mannitol: 3.06 to 8.25, p=0.008
				
				Overall proportion of lactoferrin was 23% initially. At 1 mo follow-up, there was no difference in prevalence between vitamin A (33%) and placebo (31%) groups.
				
				Cytokine concentrations did not significantly differ between placebo and vitamin A groups.
					Frequency of stool lactoferrin varied between 23%-32%.
					
					While vitamin A supplementation was associated with reduced lactulose excretion, it was also associated with reduced mannitol excretion, with no overall effect on L:M.
					
					Vitamin A supplementation was not associated with presence of lactoferrin or intestinal cytokine response.
						Authors did not report testing for associations between urinary markers of intestinal permeability and concentrations of fecal cytokines, or between these markers and growth parameters or parasitosis.
						
						Cut-point values for lactoferrin positivity and abnormal L:M were not described.
						
						Exclusively breastfed children were excluded from study participation due to assessment of stool lactoferrin.

[51] For lactulose and mannitol results, excretion measurement was not specified.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments

2005
 	
Lima AA et al.
 	
Intestinal barrier function and weight gain in malnourished children taking glutamine-supplemented enteral formula
 	
L:M as a marker of intestinal permeability and various stool tests among children with malnutrition or PD who received either glycine or glutamine supplemented formula or placebo
	Fortaleza, Brazil
	
	2-60 mo olds hospitalized with WAZ score <-2, ~70% of whom had PD.
		RCT
		
		n=80;
		
		n=53 received supplemented formula
		• 27 with glycine
		• 26 with glutamine
		
		n=27 received nonsupplemented formula
			<u>Urine Tests*</u>:
			• Lactulose[52]
			• Mannitol
			• L:M
			
			<u>Stool Tests**</u>:
			• Lactoferrin
			• Leukocytes
			• Occult blood
			• Reducing substances (RS)
			
			* n=80 tested at enrollment, n=65 tested at day 10.
			
			** n=60 tested.
				Mean[53] L:M (SE):
				• Glutamine group:
				  • Baseline: 0.31 (0.10) (similar in all three groups)
				  • Day 10: 0.10 (0.02); significant decrease, (p=0.01)
				• No significant decrease in L:M in glycine and nonsupplemented formula groups at day 10
				
				Mean lactulose (SE):
				• Glutamine group:
				  • Baseline: 0.97 (0.46) (similar in all three groups)
				  • Day 10: NS decrease in all 3 groups
				
				Mean mannitol (SE):
				• Glutamine group:
				  • Baseline: 3.42 (0.64) (similar in all three groups)
				  • Day 10: NS decrease in all 3 groups
				
				Proportion of stool markers at baseline among all subjects:
				• Lactoferrin: 53.3%
				• Leukocytes: 11.7%
				• RS: 3.3%
				• Occult blood: 5.0%
					L:M significantly improved in the glutamine group only.
					
					>50% of subjects had intestinal inflammation by stool lactoferrin. Fecal leukocytes, RS, and occult blood were detected in fewer subjects than lactoferrin.
						The relationship between stool markers and L:M was not reported.
						
						Data were not stratified by history of PD.
						
						Fecal fat was assessed, but results were not reported.
						
						Cut-off values for lactoferrin positivity were not described.
						
						Exclusively breastfed children were excluded from study participation due to assessment of stool lactoferrin.

[52] Lactulose and mannitol results were expressed as % of dose administered.
[53] Type of mean not specified.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
2007 Lima NL et al. Wasting and intestinal barrier function in children taking alanyl-glutamine-supplemented enteral formula L:M as a marker of intestinal permeability in assessing alanyl-glutamine supplement to improve intestinal barrier function in malnourished children compared to glycine-containing placebo supplement	Parque Universitario, Fortaleza, Brazil 6 mo-8 yr olds (mean age 3.5 yr) from an urban setting with HAZ, WAZ, or WHZ scores <-1.	RCT n=107; n=51 received alanyl-glutamine treatment n=56 received glycine placebo	<u>Urine Tests</u>: • Lactulose[54] • Mannitol • L:M	L:M median (range) at baseline: • Treatment: 0.0385 (0.8922 [sic]) • Placebo: 0.0302 (5.5812 [sic]) Lactulose and mannitol excretion both significantly decreased in the treatment group only (p=0.05 for both sugars)[55]. L:M did not change significantly within or across groups days after treatment. Lactulose excretion was not associated with WHZ, WAZ or HAZ scores in either group[56]. Mannitol was not associated with growth parameters in the control group, but was associated with WHZ (r^2=-0.386, p=0.027) and WAZ (r^2=-0.385, p=0.027) scores in the supplemented group. Data for L:M and growth parameter association was not provided.	Even though lactulose excretion improved in the treatment group, mannitol excretion worsened with overall L:M not changing. Lactulose, mannitol and L:M did not change significantly in the placebo group.	Authors state that L:M median and range values were within the confidence interval for values of healthy children in the study community; no reference was cited. Although the authors defined persistent and chronic diarrhea in their methods, they did not report data stratified according to these conditions. Authors provide negative R^2 values when reporting Pearson's correlation analysis results; these likely actually represent r values.
2006 Long KZ et al. The effect of vitamin A supplementation on the intestinal	Mexico City, Mexico All 5-15 mo olds within a periurban community were eligible to be	RCT n=505 stool samples from 127 children; n=243 stool	<u>Stool Tests</u>: Cytokines: • IL-4 • IL-6 • IFN-γ	Positive tests for fecal cytokines: • IL-4: ~55% • IFN-γ: ~50% • IL-6: ~40% There were no significant	Differences in fecal cytokine concentrations due to vitamin A supplementation were observed only in the subset	Pre-intervention fecal cytokine concentrations were not reported. Differences in fecal cytokines between all subjects with

[54] For lactulose and mannitol results, excretion measurement was not specified.
[55] Reported results were adjusted for age and season.
[56] Reported results were adjusted for age and season.

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Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
immune response in Mexican children is modified by pathogen infections and diarrhea Fecal cytokines as markers of intestinal mucosal immune activation in children with and without GI pathogens receiving vitamin A or placebo	screened for participation.	samples from 57 who received vitamin A supplementation n=262 stool samples from 70 who received placebo Participants were followed regularly; diarrhea history was tracked and stool samples were tested.		differences in proportions of these fecal cytokines between vitamin A-supplemented and placebo subjects. Vitamin A-supplemented children with diarrhea had lower median IFN-γ concentrations (odds ratio[57]=0.51; CI: 0.26, 0.99) and higher IL-4 concentrations (odds ratio=2.14; CI: 0.94, 4.87) compared to children with diarrhea in the placebo group in a nonrandomized analysis. IL-6 concentrations did not differ in this analysis. There were no differences between the two groups among those without diarrhea. Differences in median concentrations of fecal cytokines by types of enteric pathogens were also observed.	of subjects with GI infection or diarrhea.	and without GI infections or history of diarrhea were not directly reported; all differences were described in terms of vitamin A interaction.

2005
 	
López de Romaña D et al.
 	
Longitudinal measurements of zinc absorption in Peruvian children consuming wheat
	Lima, Peru
	
	3-4 yr olds residing in a poor community at the periphery of Lima with stunting and moderate anemia as a surrogate risk factor for zinc
		RCT
		
		n=41;
		(31 completed both initial and follow-up absorption assay at 2 mo)
		
		Group 1:
			Urine Test:
			Zinc excretion to measure fractional absorption of zinc (FAZ) and total absorbed zinc (TAZ) following radiolabeled zinc administration
				Mean zinc parameters (SD) at initial assessment:
				• FAZ:
				  • Group 1: 0.34 (0.11)
				  • Group 2: 0.24 (0.05)
				  • Group 3: 0.13 (0.04)
				• TAZ (mg/d):
				  • Group 1: 0.71 (0.18)
				  • Group 2: 1.11 (0.21)
				  • Group 3: 1.34 (0.47)
					Despite a reduction in FAZ with increasing fortification, TAZ increased as more zinc was consumed and with increasing concentrations of zinc fortification.	Intestinal function could play a role in zinc (or other micronutrient) absorption; such factors were not explored in this study.
						
						The principal aim

[57] The odds ratios represent odds that a cytokine (categorized into three levels: undetectable, <median, >median) will have a higher value among vitamin A-supplemented children.

Appendix 7. Evidence table of all studies included in the review.

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products fortified with iron only or iron and 1 of 2 amounts of zinc Zinc absorption among stunted, anemic children receiving zinc as well as iron and/or iron/zinc-fortified foods	deficiency.	n=14 received wheat flour with iron fortification only (10 completed follow-up) Group 2: n=12 received wheat flour with iron and 3mg zinc/100g flour (9 completed follow-up) Group 3: n=15 wheat flour with iron and 9mg zinc/100g flour (12 completed follow-up)		Neither mean FAZ nor TAZ changed significantly at subsequent assessments in any treatment group. In both the initial and subsequent assays, mean TAZ from zinc-fortified meals increased with increasing amounts of fortification ($p< 0.001$). However mean FAZ was inversely related to zinc intake from these meals ($p<0.001$). Nonfortified dinner FAZ and TAZ were significantly lower in the group receiving the most zinc-supplementation at the initial assay ($p=0.015$ and $p=0.012$, respectively) despite no difference in zinc intakes from the unfortified dinner by treatment group. This relationship between groups was not observed at the second assay; however, a significant decrease of 16% in mean FAZ and TAZ from the unfortified dinners was observed between initial and subsequent assays ($p<0.001$). Mean plasma zinc concentrations did not differ between treatment groups throughout the study period. The proportion with low fasting plasma zinc concentrations (<65µg/dL)	Authors speculate that reduction in FAZ with increasing fortification could be due to factors such as saturation kinetics. Authors described a unexpected finding: subjects consuming more zinc from the zinc-fortified breakfast and lunch meals absorbed less zinc from the unfortified dinners during the initial absorption assay.	of this study was to determine appropriate extent of zinc fortification of a staple food in a specific community; we present only results relevant to this review.

Appendix 7. Evidence table of all studies included in the review.

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				was lower at the end of the study (3.3% vs. 20.5% initially, p=0.046).		
2001 Mahmud MA et al. Sociodemographic, environmental and clinical risk factors for developing persistent diarrhea among infants in a rural community of Egypt Stool IgE as a marker of gastrointestinal allergy and its association with persistent vs. acute diarrhea	Bilbeis, Egypt Newborns recruited at birth from a rural village and followed for the first year of life. Surveillance of diarrhea symptoms identified 392 episodes of diarrhea, 41 (11%) of which were persistent.	Nested case-control within a cohort study n=392 episodes of diarrhea (including 41 episodes of PD) among 152 infants*) * Stool samples from each PD episode were counted as a case for analysis and compared to randomly selected AD episodes and to non-diarrheal samples.	Stool Test: IgE	Fecal IgE was detected more frequently in stools from episodes of PD compared to episodes of AD: odds ratio (CI)[58]=3.3 (1.0, 10.9). Fecal IgE was detected more frequently in stools from episodes of PD than in stools from children without diarrhea: odds ratio (CI)=4.84 (1.1, 21.7).	Fecal IgE was detected 3 times more frequently during episodes of PD than AD and 5 times more frequently in PD stools than in stools from those without diarrhea.	Sampling was based on episodes of diarrhea within a cohort of infants; individual infants could have contributed more than one diarrheal episode. Additionally, it appears that an individual could also have been included as a case of PD, a control with AD, or a non-diarrhea stool within the same analysis. Study population appears to be the same as in another Mahmud, et al. study also included in this review which reported the prevalence of fecal IgE by gender and age within the cohort [143].
2001 Mahmud MA et al.	Bilbeis, Egypt Newborns recruited at birth	Cohort n=152 followed for	Stool Test: IgE	Overall incidence of fecal IgE: 0.39/child-year By age group:	Substantial incidence of fecal IgE was observed in this setting in	Study population appears to be the same population as in another

[58] Reported results were adjusted for confounding variables, unless otherwise noted.

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Increased fecal IgE among infants in a rural community of Egypt: an analysis of associated risk factors Fecal IgE as a marker of intestinal inflammation among children with diarrhea	from a rural village and followed for the first year of life.	29,036 infant days Stools were collected during episodes of diarrhea.		• < 3 mo: 0.28/child-yr • 3-6 mo: 0.42/child-yr • 6-9 mo: 0.16/child-yr • >9 mo: 0.12/child-yr Relative risks (CI): • 3-6 compared to >9 mo olds : 3.28 (1.03, 13.60) • Male gender: 1.82 (0.83, 4.18)	infants. IgE incidence peaked at 3-6 mo of age. Male gender was associated with fecal IgE.	Mahmud, et al. reference also included in this review which assessed the relationship between fecal IgE and PD [142].
2002 Manary ML et al. Zinc homeostasis in Malawian children consuming a high-phytate, maize-based diet Zinc absorption in a sample of 10 asymptomatic children	Blantyre, Malawi 2–5 yr olds (mean age 43.6 mo, SD 7.7) from rural area attending immunization clinic. There was a high prevalence of stunting and low plasma zinc in this series.	Case-series n=10	<u>Stool Test</u>: Endogenous fecal zinc (EFZ) <u>Urine Test</u>: Zinc excretion to measure fractional absorption (FAZ) and total absorption (TAZ) following radiolabeled zinc administration.	Mean (SD): • FAZ: 0.24 (0.04) • TAZ (mg/d): 1.30 (0.33) • EFZ (mg/d): 1.15 (0.33) Language in the discussion section strongly suggests, but does not explicitly state, that TAZ and EFZ were not correlated. Correlation analysis for these parameters was not reported.	EFZ was higher than would be expected for a zinc deficient cohort, and EFZ was not correlated with TAZ as would have been expected. While high-phytate diets leading to poor zinc absorption might explain these findings, the authors note that in a previous study (among a somewhat older age group) there were no differences in EFZ among children consuming high- or low-phytate diets [187]. They note that such perturbations in EFZ have also	Authors note that the lack of comparable data from children of the age range in this study limits data interpretation. They also provide results per body weight due to presumed relationship; validity of such measures has not been established. Authors comment that the methods used for calculating absorption measures are sensitive and accurate, but quite difficult to conduct, especially among children.

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					been reported in children with enteropathy due to cystic fibrosis [188] and suggest that a similar process could be going on in these Malawian children due to TE.	
2001 Mishra OP et al. Endoscopic and histopathological evaluation of preschool children with chronic diarrhea Duodenal biopsy among patients with chronic diarrhea	Varanasi, India 1-5 yr olds with PD selected randomly from an outpatient population in an urban setting. A high proportion of the children had varying degrees of protein energy malnutrition.	Case-series n=30 with endoscopy performed	<u>Endoscopic duodenal biopsy:</u> • Gross endoscopic visualization • Histopathology	7 (23.3%) had grossly abnormal endoscopic findings: • 5 (16.7%) with chronic duodenitis • 1 with duodenitis with multiple erosions • 1 with duodenitis with hemorrhagic gastritis 22 (73.3%) had abnormal histopathology: • 17 (56.7%) with villous atrophy with mononuclear cell infiltration • 1 (3.3%) with villous atrophy and eosinophilic infiltration • 2 (6.7%) with villous atrophy and mononuclear and eosinophilic infiltration • 2 (6.7%) with only mononuclear cell infiltration Mean duration of diarrhea (SD) was not associated with gross endoscopic	Grossly abnormal endoscopic appearance was found in one-quarter of children with chronic diarrhea assessed by endoscopy. Three-quarters had abnormal histology. More than half had villous atrophy with mononuclear cell infiltration; these patients had >1 month longer duration of diarrhea than those with either normal histology or mononuclear cell infiltration without villous atrophy. Age, enteropathogen recovery, and WFA were not	Authors do not report assessing relationship between gross endoscopic findings and histopathology. Number of patients with villous atrophy and both mononuclear and eosinophilic infiltration was very small (n=2), yet authors report a significant difference in their duration of diarrhea relative to those with normal histopathology.

Appendix 7. Evidence table of all studies included in the review.

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				findings but did vary by histopathology: • Normal histopathology: 9.0 wk (6.0), n=8 • Mononuclear cell infiltration: 9.0 wk (6.0), n=2 • Villous atrophy with mononuclear cell infiltration: 14.9 wk (5.3), n=17, p<0.02 compared to normal histopathology • Villous atrophy with mononuclear and eosinophilic infiltration: 21.5 wk (2.1), n=2, p<0.02 compared to normal histopathology • Villous atrophy with eosinophilic infiltration: 6.0 wk, n=1 No consistent pattern was observed between gross endoscopic findings or histopathological lesions and age, degree of malnutrition, or type of enteropathogen recovered in stools.	associated with gross endoscopic or histopathological findings.	
2001 Mittal SK et al. Tropical sprue in north Indian children D-xylose and duodenal biopsy as	New Delhi, India 0-15 yr old gastroenterology clinic patients with PD. Those with	Case-series n=94; (38 with repeat biopsies) <5 yr old: n=44	<u>Duodenal biopsy, method not specified:</u> Histopathology <u>Blood Tests</u>: • Hemoglobin • **D-xylose***	36 (38.3%) were diagnosed with TS including 14/44 (31.8%) who were under 5 years of age. 18 (19.1%) were diagnosed with CD. Degree of villous atrophy	More than half of the GI clinic patients with PD had some degree of villous atrophy. More than one-third and almost one-fifth of	Biopsy results were not provided for patients without TS or CD. It was unclear if there were patients with abnormal D-xylose and

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
markers of TS	abnormal morphology on biopsy, abnormal D-xylose test, and clinical response to antibiotics were diagnosed as having TS. Those with abnormal morphology and response to gluten-free diet were diagnosed with CD. We include data on these subjects for comparative reasons.		* Not specified whether from urine or serum, and units of measurement not provided.	among TS vs. CD patients: • Mild in 8/36 (22.2%) vs. 0 • Moderate in 23/36 (63.9%) vs. 4/18 (22.2%) • Severe in 5/36 (13.9%) vs. 14/18 (77.8%) Mean hemoglobin concentration (range) among TS patients was 8.3 g/dL (5.5-11) and did not differ from values of those with CD. Among the 22 TS patients, repeat biopsies showed: • 16 with normalization • 5 with improvement • 1 worsened despite marked clinical improvement The D-xylose test was abnormal in all TS patients by diagnostic definition.	subjects were diagnosed with TS and CD, respectively. By study diagnostic definition, all TS patients improved with treatment. Among those who had repeat biopsies, almost three-quarters showed normalization of histology, while 23% had partial improvement and 1 patient had worsened pathology.	histology who did not respond to antibiotic therapy and therefore were not diagnosed with TS. Cut-off points used to define abnormal D-xylose tests were not provided.
2002 Moya-Camarena SY et al. Effects of asymptomatic *Giardia intestinalis* infection on carbohydrate absorption in well-nourished Mexican children	Hermosillo, Sonora, Mexico 3-6 yr olds in a periurban setting attending preschool centers meeting inclusion criteria of no GI symptoms, no antibiotics in the preceding 3 wk, and no SBBO by lactulose HBT and	Case-control n=13; <5 yr old: n=5 n=7 asymptomatic cases infected only with *G. intestinalis* n=6 controls	Breath Tests*: • Lactose HBT • D-Xylose HBT** Urine Test: D-xylose**,[59] * Reported as parts per million (ppm) post-substrate ingestion after subtraction of baseline, pre-	Mean lactose HBT (SE): • Cases pre-treatment: 3.6 (0.75) ppm • Cases post-treatment: -0.85 (0.75) ppm ($p<0.05$ compared to pre-treatment) • Controls: 0.19 (0.81) ppm ($p<0.05$ compared to pre-treatment cases) Mean xylose HBT (SE): • Cases pre-treatment: 2.2 (0.69) ppm for infected	Lactose HBT concentrations were normal according to established cut-points among all subjects. However, lactose HBT was significantly higher among cases compared to controls and	Statistical methods might not have been adequate to account for intra-subject correlation when comparing the same group of subjects (cases) before and after treatment. Investigators wished to exclude children with

[59] D-xylose results were expressed as % of dose administered.

Appendix 7. Evidence table of all studies included in the review.

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Lactose hydrogen breath test (HBT) as a marker of lactose absorption, and xylose breath test and urinary excretion as markers of xylose absorption in well-nourished children with asymptomatic giardiasis and non-infected controls	Indican test.	without *Giardia* Cases were evaluated before and 3 wk after treatment with tinidazole. Post-treatment stools were verified for absence of parasites.	substrate H_2 concentrations. A positive HBT is considered to be a rise of $\geq$20ppm in breath H_2 above baseline H_2 concentration. ** Investigators did not specify the xylose enantiomer used, however test functionality characteristics lead us to assume that it was the dextrorotary (D) enantiomer.	group • Cases post-treatment: -4.16 (0.69) ppm ($p<0.05$ compared to pre-treatment) • Controls: 1.13 (0.74) ppm (NS compared to pre-treatment cases) Mean urinary excretion of xylose (SE) among cases pre-treatment and post-treatment was 34% (3) and 46% (11), respectively (NS), well above cut-offs indicative of malabsorption.	there was also a significant decrease in lactose HBT among cases after treatment. The clinical relevance of such mildly elevated HBT results in asymptomatically infected children is unclear. Results did not demonstrate xylose malabsorption by either urinary or breath measures among any group. While urinary results did not differ before and after treatment, case xylose HBT was significantly lower after treatment; again the clinical significance of such results is not apparent.	SBBO. As such, inclusion criteria restricted participants to those with adequate production of H_2 following ingestion of lactulose and with minimal urinary indoxyl sulfate excretion. The number of children excluded due to failure to meet these criteria was not reported.
2002 Murphy JL et al. Maldigestion and malabsorption of dietary lipid during severe childhood	Kingston, Jamaica 5-23 mo olds admitted to the Tropical Metabolism Research Unit of the University of	Case-series n=24 Subjects were divided into 3 groups of 8	<u>Stool Tests</u>: • Total and fractionated ^{13}C following ingestion of one of three ^{13}C labeled triglycerides (TG): trilaurin, triolein, or trilinolein*	Median total stool excretion of ^{13}C in phase 1 was 9% (range: 1%-29%) and did not vary between TG groups. Median ^{13}C excretion dropped 33%-99% in phase 2 and 86%-95% in phase 3	High concentrations of ^{13}C (compared to healthy UK children) [190] were observed in half of the subjects at	Authors state that the study was not powered to compare the different TGs, but they contend that medium chain trilaurin did not

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Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
malnutrition Stool recovery of radiolabeled products as markers of lipid digestion and absorption, and bile salt deconjugation as a marker of SBBO among children with severe malnutrition	the West Indies with severe malnutrition.	children, each group receiving a different labeled triglyceride. Data were collected in three separate phases as described above in JL Murphy et al. 2001 [149].	• ^{13}C stool assay following administration of labeled fatty acid ^{13}C glycocholate** * To assess fat excretion as a % of dose administered. Also assessed proportion of ^{13}C in triglyceride (TG) and fatty acid (FA) fractions to distinguish excretion caused impaired digestion (presence of TG) vs. poor absorption (presence of FA). ** To assess bile salt deconjugation in the bowel caused by SBBO; conducted after the TG assessment and a 3 day washout period.	compared to phase 1 ($p<0.05$ each). Over the study period, there were significant associations between total lipid and the amount of ^{13}C labeled TGs in stool for some groups, but not for others. Median ^{13}C in TG and FA was similar across TG groups in all phases. 13C FA recovery was similar and reduced by ~2/3 compared to Phase 1. ^{13}C TG was not detectable in Phases 2 or 3. Statistical comparisons between phases were not reported. ^{13}C after radiolabeled glycocholate administration was detected in stool at quantities considered to be in excess of the 7% recovery of dose administered upper limit of normal in U.S. adults in [189]: • Phase 1: 13/24 (54%) • Phase 2: 5/24 (20.8%) • Phase 3: 3/24 (12.5%)	admission, reflecting impaired digestion or absorption. The differences in stool ^{13}C were wide but not as extreme as in a previous study by same investigators (also examined in this review) using a different TG (tripalmitin) substrate [149]. ^{13}C excretion did not significantly differ between TG groups and declined with improving clinical course. Similar to their previous study, significantly more ^{13}C in stool was recovered as FA than TG, reflecting impaired absorption over poor lipid digestion/ hydrolysis. Unlike in their previous study, there was evidence of SBBO as	appear to be processed differently than the longer chain TGs triolein and triolinolein. Authors did not describe the method used to assign subjects to different TG groups. While it was noted that some subjects had positive stool cultures, details were not provided on the nature of the enteric infections.

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					measured post-ingestion of ^{13}C glycocholate.	
2001 Murphy JL et al. Gastrointestinal handling and metabolic disposal of ^{13}C-labelled tripalmitin during rehabilitation from childhood malnutrition Fecal fat, stool recovery of radiolabeled products, and breath tests as markers of lipid digestion and absorption and bile salt deconjugation as a marker of SBBO among children with severe malnutrition	Kingston, Jamaica 7-23 mo olds with malnutrition admitted to the University of the West Indies.	Case-series n=8 Data were collected in three separate phases (each lasting 9 days): 1. Within 48 hours of admission 2. During early rehabilitation 3. During late rehabilitation	<u>Stool Tests</u>: • Fecal fat* • Total and fractionated ^{13}C assay after administration of ^{13}C tripalmitin (TP)** • ^{13}C assay after administration of ^{13}C glycocholate (GCA)*** <u>Breath Tests</u>: • $^{13}CO_2$ after administration of ^{13}C glycocholate (GCA)*** • $^{13}CO_2$ after administration of ^{13}C TP**** * In 72 hour stool collection (measured as total grams and as % of dietary fat intake). ** To assess fat excretion as a % of dose administered. Also assessed proportion of ^{13}C in triglyceride (TG) and fatty acid (FA) fractions to distinguish	Mean fecal fat (SD): • Phase 1: 2.4 g/day (3.6) or 5.9% (9.4) of dietary lipid intake • Phase 2: 1.7 (0.9) g/day, or 3.3% (2.4) of intake • Phase 3: 0.9 (0.6) g/day, or 1.4% (0.7) of intake • Differences between phases were not statistically significant. Total excretion of ^{13}C in stool also varied widely across patients (0%-44%) and did not differ between study phases. Correlation between fecal fat and ^{13}C ($r=0.48$; $p<0.05$) was observed. Lack of lipid digestion and absorption were assessed by measuring TG and FA fractions, respectively. Mean ^{13}C TG recovery (SD) (% of administered dose), number of patients excreting TG: • Phase 1: 0.7% (1.6), n=3 • Phase 2: 0.9% (2.8), n=1 • Phase 3: no recovery from any subjects, differences between phases were NS ^{13}C FA fraction in stool	Mean fecal fat was not elevated compared to published norms [191, 192] during any study phase. There was wide variation in fecal fat at presentation, and wide variations in stool ^{13}C across subjects. Authors indicate that this is the first such assessment in malnourished children; previous studies on healthy children from the UK demonstrated average excretion of 6% [190]. The majority of excreted ^{13}C was in the form of FA rather than TG. Authors interpreted this to reflect failure of lipid absorption in the face of adequate digestion/ hydrolysis. Each form (FA and TG)	Statistical methods might be inappropriate for a small sample. All subjects were treated with antibiotics including metronidazole for presumptive SBBO; this might have affected GCA testing.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
			excretion caused by impaired digestion (presence of TG) vs. poor absorption (presence of FA). *** To assess bile salt deconjugation in the bowel caused by SBBO; conducted after the TG assessment and a 3 day washout period. **** Expressed as a percentage of absorbed label (dose administered - label recovered in stool) to assess oxidation for acute energy needs.	declined during rehabilitation. Mean ^{13}C FA recovery (SD): • Phase 1: 6.0% (7.3) • Phase 2: 4.8% (3.7) • Phase 3: 3.3% (3.8), differences between phases were NS Mean FA values were ~9x (NS), 5x ($p<0.001$), and 3x ($p<0.05$) higher than mean TG values in Phases 1, 2, and 3, respectively. Following administration of labeled TP, absorbed ^{13}C label by breath analysis was ~5% (range 0%-21.2%) and similar across study phases. Following the administration of labeled GCA, there was either no or minimal recovery of ^{13}C in stool and $^{13}CO_2$ on breath (as % of dose administered) in all phases.	was found in decreasing values as the study phases progressed, suggesting improved digestion and absorption, although results did not differ significantly. Fecal fat was correlated with concentrations of ^{13}C in stool. There was no evidence of SBBO or bile acid malabsorption. $^{13}CO_2$ excretion following administration of ^{13}C TP was minimal, suggesting a propensity for deposition in adipose tissues rather than oxidation for immediate energy needs. The authors report that this breath test has not been widely used, but that healthy UK children have breath excretion	

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					values from 15%-43% [190], compared to a mean of 5% and range 0%-21% in this cohort; the latter findings were more similar to results from kwashiorkor patients where ^{13}C-labeled oleic acid was used as substrate [193].	

2000
 	
Nichols B et al.
 	
Contribution of villous atrophy to reduced intestinal maltase in infants with malnutrition
 	
Jejunal biopsy, maltase activity, and enzyme messenger RNAs among malnourished and well-nourished children. Assessed association between maltase and villous atrophy and other mucosal intestinal markers indicative of loss of enterocytes and enterocytic function.
	Sao Paulo, Brazil
	
	Cases were children (mean age 9.9 mo, SD 8.1) hospitalized with malnutrition refractory to dietary rehabilitation.
	
	Controls were children (mean age 3.6 mo, SD 1.0) with HAZ and WAZ scores >-2 and normal intestinal mucosa on biopsy, hospitalized for Kasai procedure for biliary atresia.
		Case-control
		
		n=33;
		
		n=24 cases
		
		n=9 controls
		
		Subjects were matched on height and weight; ages differed within matched sets.
			<u>Jejunal capsule biopsy:</u>
			• Histopathology*
			• Maltase activity
			• Intestinal messenger RNA (mRNA) abundances:
			  • Maltase-glucoamylase (MGA)
			  • Sucrase-isomaltase (SI)
			  • Villin, a structural protein expressed only in enterocytes
			  • Sodium-activated luminal glucose-galactose transporter 1 (SGLT), a functional protein expressed only in enterocytes
				Mean villous atrophy score (SD):
				• Cases: 2.6 (0.8)
				• Controls: 1.2 (0.5), p=0.006)
				
				WAZ score was correlated with villous atrophy (r=0.65, p- value not reported).
				
				13/25 [sic] cases and 0/5 controls had subnormal (defined as <94 U/g protein) of maltase activity; mean maltase was 34% lower among cases (p=0.11). Maltase activity did not appear to decrease with WAZ score (further details not provided).
				
				However, in sub-analyses among those samples with an adequate β-actin, a housekeeping gene message, (n=10 cases, n=9 controls), cases' findings
					The malnourished children had significantly greater villous atrophy than the younger controls.
					
					Among the subset tested for mRNA messages, maltase activity as well as the mRNA abundances for MGA, villin and SGLT were significantly correlated with case status and were correlated with villous atrophy.
					
					While maltase deficiency has been reported in malnutrition in
						Tissue from patients requiring intestinal resection as part of their biliary atresia management provides an opportunity to assess presumably "normal" intestinal architecture. However, unless they mocked up *ex vivo* mucosal biopsies in these controls, resections will have lower proportions of villous to submucosa tissue compared to cases' samples derived from mucosal biopsies. While this probably doesn't affect histology, it might affect

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			• β-actin * Mucosal atrophy was scored on a scale of 1 (absence of atrophy compared to an organ donor) to 4 (similar to children with active CD). Histology among controls was on surgically resected tissue.	expressed as a mean percent of controls' (SD) included: • Villous length (reciprocal of atrophy score): 38.9 (41.6), p=0.004 • Maltase activity: 37.1 (23.2), p=0.001 • MGA mRNA: 45.1 (36.4), p=0.016 • Villin mRNA: 52.5 (22.6), p=0.003 • SGLT mRNA: 66.6 (23.1), p=0.057 • β-actin: 88.2 (15.8), p=0.189 Both villous length and maltase activity in a subset of cases were less than 40% of control values. MGA, villin, and SGLT mRNA abundances were correlated with villous atrophy score (r=0.73), (r=0.76), and (r=0.54), respectively (p-values not reported)[60]. MGA mRNA abundance was correlated with maltase activity (r=0.32).	other studies, authors assert that these are the first results that directly support the hypothesis that reductions in maltase activity are due to villous atrophy. This study also nicely correlates mRNA relative abundance with function.	enterocyte functional assays and mRNA determination, as transmural tissue will bring in more diverse populations of cells; only some of them might have transcripts of interest. However, the bias is likely in a direction that would reduce effect size. It was unclear if control inclusion criteria included absence of atrophy or if all potential controls lacked atrophy. Statistical methods might not have adequately taken into account the small sample size and matching scheme. Subsets of subjects were investigated for various tests. For example, 10 cases had mRNA analyses based on β-actin adequacy. Another instance of

[60] Villin and SGLT1 were assessed as a ratio with housekeeper gene β-actin.

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						selected testing was the subset of 22 and 15 cases that had WAZ score to histology and mRNA correlation analyses, respectively. Rationale for subset selection was not thoroughly described.
2001 Northrop-Clewes CA et al. Anthelmintic treatment of rural Bangladeshi children: effect on host physiology, growth, and biochemical status L:M as a marker of intestinal permeability, and α 1-antichymotrypsin as a marker of inflammation and immune response to treatment among children randomized to bimonthly antihelminthics or placebo.	Jamalpur district, northern Bangladesh 2-5 yr olds from poor rural villages, sampled randomly from a larger cohort study. Stools were assessed for helminthiasis and giardiasis. Growth was followed longitudinally.	RCT* n=109; n=54 received bimonthly empiric antihelminthic treatment n=55 received placebo * Randomized at the village level.	<u>Blood Tests</u>: • α 1-antichymotrypsin (ACT) • Albumin • Total protein <u>Urine Test</u>: L:M Among 93 subjects with L:M at baseline: • 46 received treatment • 47 received placebo Among 66 subjects with repeated L:M testing: • 34 received treatment • 32 received placebo	Mean L:M[61] at baseline: • Treatment: 0.22 • Placebo: 0.25 Seasonal variation in L:M was observed, with highest values following the monsoon season. Within-subject L:M analysis showed no significant association with intestinal helminthiasis and no significant improvement in treatment or placebo groups over 1 yr. L:M was generally not associated with giardiasis (with the exception of one group at one study interval). L:M was inversely correlated with ΔHAZ and ΔWAZ scores at some of the follow-up intervals (r=-0.22, p<0.02 and r=-0.21,	L:M ratios were high overall and demonstrated seasonal variation. Intra-individual L:M values did not change significantly over time, nor were they associated with helminthiasis or consistently associated with giardiasis. Inverse correlations were seen between L:M and growth parameters. Serum markers were within normal range.	Baseline study data were lost, so analysis began with samples taken at month 2. The relationship between the serum markers and intestinal permeability was not reported.

[61] Geometric mean.

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				p<0.05, respectively, at 12 mo follow-up visit). Mean serum ACT, albumin and total protein were within normal ranges and were not associated with growth parameters. ACT and albumin concentrations did not significantly change with treatment, whereas total protein concentrations did (p<0.001).	The only significant change in these markers was a decrease in total protein in the treatment group without concomitant change in albumin; this suggested a decrease in globulins (not directly measured), perhaps due to decreased inflammation.	
2009 Panter-Brick C et al. Pathways leading to early growth faltering: An investigation into the importance of mucosal damage and immunostimulation in different socio-economic groups in Nepal Lactose:creatinine ratio (Lactose:Cr) as a marker of intestinal permeability and	Kathmandu, Nepal 3-18 mo olds in two cohorts: 1. All children in target age range from four squatter settlements 2. Randomly selected, age-matched cohort from lower middle-class, periurban households	Cohort n=86; n=48 in squatter cohort n=38 in lower middle-class cohort	Urine Test: Lactose:Cr Blood Test: • Hemoglobin	Mean[62] Lactose:Cr (CI): • Squatter: 0.14 (0.12, 0.16) • Middle Class: 0.08 (0.07, 0.10) • Statistically significant difference between the 2 groups among the 6-12 mo olds (p=0.007) and 18-24 mo olds (p=0.002), but not among 12-18 mo olds. • For both SES groups, Lactose:Cr values decreased with increasing age (p<0.001). HAZ, WAZ, WHZ, and ΔWAZ scores were strongly associated with mean Lactose:Cr (p<0.001 each)	Authors speculate that Lactose:Cr accounted for less of the deterioration in nutritional status among the squatter children because of several factors, including poorer nutritional intake, that impact the nutritional status of children with lower socio-economic status.	Specific sugar excretion was normalized to urinary creatinine to control for variation in renal function. Authors suggest that while Lactose:Cr might not be as accurate as L:M, it might be a more field-friendly assessment of mucosal damage compared to L:M, requiring only spot urine collection and no substrate

[62] Geometric mean.

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hemoglobin, albumin, α-1-acid glycoprotein, and IgG as markers of immunostimulation. The latter were also assessed for their relationship to nutritional status.				as was ΔHAZ score (p=0.004); ΔWHZ score was not. The strength and magnitude of association between ΔWAZ score and Lactose:Cr was most pronounced among the wealthier cohort and there was no association between ΔHAZ score and Lactose:Cr among the squatter children. Hemoglobin concentrations were inversely related to Lactose:Cr (r^2=0.018, p<0.001).		dosing. However, L:M was not assessed in this study; direct comparison of the two tests was not possible. While hemoglobin concentration was inversely related to Lactose:Cr, testing for associations of other measured blood markers (IgG, AGP and albumin) with Lactose:Cr were not reported.
2001 Perin NM et al. Intestinal absorption of D-xylose in children infected with the human immunodeficiency virus D-xylose as a marker of intestinal absorption among HIV-infected children with and without GI symptoms	Florianopolis, Brazil 18 mo-14 yr old HIV-infected children with GI and non-GI symptoms of HIV infection recruited from a pediatric AIDS center.	Cross-sectional n=104	Blood Test: D-xylose	Prevalence of an abnormal D-xylose result was 7.7%. Mean D-xylose (SD, range): 42.8mg/dL (14.4mg/dL, 16-73 mg/dL) D-xylose was not associated with age. Of the 8 children with abnormal results, 1 had diarrhea. Of 19 with diarrhea, 1 had an abnormal result. Of those with abnormal results, 50% had *Cryptosporidium* infection. Of the 33 subjects with *Cryptosporidium* infection, 4 had abnormal D-xylose	D-xylose showed substantial variation across individuals.	Portuguese language article. D-xylose <25 mg/dL was defined as indicative of malabsorption.

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				results.		

2003
 	
Pires AL et al.
 	
Digital morphometric and stereologic analysis of small intestinal mucosa in well-nourished and malnourished children with persistent diarrhea
 	
Computerized morphometric and stereologic assessments in proximal small intestine biopsy in subjects with PD
	Porto Alegre, Brazil
	
	6 mo-5 yr old inpatients from an urban setting who underwent biopsy as part of a work-up for PD.
	
	There was a high proportion of children with malnutrition in this study population.
		Cross-sectional, retrospective
		
		n=65
			<u>Small intestinal biopsies, site and method not specified*:</u>
			• Mucosal morphometric assessment by computer analysis (62 tested):
			  • Villous height
			  • Crypt depth
			  • Villous:crypt ratio
			  • Mucosal thickness
			• Digital assessment (500x magnification) (65 tested):
			  • Enterocyte height
			  • Enterocyte nucleus height
			  • Brush border height
			• Stereological analysis to assess mucosal surface area (62 tested)
			
			* From stored specimens previously assessed by micrometer.
				Computerized mucosal measures were similar to those by micrometer and were not associated with nutritional status.
				
				Digitally assessed enterocyte height, enterocyte brush border, and enterocyte nucleus height correlations:
				• WAZ score: r=0.25 (p=0.038), r=0.26 (p=0.03), and r=0.24, (p=0.05), respectively
				• WHZ score: r=0.29 (p=0.02), r=0.27 (p=0.03), and r=0.16 (p=0.19), respectively
				• HAZ score: r=0.16 (0.18), r=0.23 (p=0.06), r=0.23 (0.06)
				
				There was no correlation between mucosal surface area and growth parameters.
					Enterocyte measures show some correlation with WAZ and WHZ scores, but not with HAZ score. However, surface area and villous:crypt ratios were not correlated with any growth parameter.	

2008 Poddar U et al.	Chandigarh, India <14 yr (mean age	Case-control n=28 controls;	<u>Endoscopic duodenal biopsy</u>: Histopathology	Duodenal biopsy of those with giardiasis showed nonspecific chronic	Duodenal biopsy demonstrated histological	Authors did not report the biopsy findings in the TS

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Is tissue transglutaminase autoantibody the best for diagnosing celiac disease in children of developing countries Duodenal biopsies in controls with giardiasis, TS, and SBBO	6.9 yr) presenting with symptoms consistent with CD (PD, FTT, and/or pallor) Subjects negative for CD were of interest for this review.	• 22 with giardiasis • 1 with TS • 5 with SBBO		inflammation of lamina propria; there was no evidence of villous atrophy.	changes accompanying *Giardia* infection.	or SBBO patients.
2002 Poddar U et al. Celiac disease in India: Are they true cases of celiac disease? Duodenal biopsy, D-xylose, and fecal fat in children with symptoms of CD but normal mucosal biopsy results	Chandigarh, India 18 mo-14 yr olds with PD, FTT, or pallor from a hospital pediatric gastroenterology unit. Subjects with normal crypt:villous ratio on biopsy were of interest for this review.	Case-control n=47	<u>Endoscopic duodenal biopsy</u>: Histopathology <u>Stool Tests</u>: • Fecal fat* • D-xylose** * In 72-hour stool collection. ** Not specified whether from urine or serum, and units of measurement not provided.	38% had chronic inflammatory cell infiltrates in the lamina propria. 55% had abnormal D-xylose concentrations. 20% had abnormal fecal fat test. No results beyond proportion positive were reported for any of the above markers.	Among controls with normal mucosal architecture by biopsy, more than one-third had PD. D-xylose and fecal fat might not correlate well with duodenal biopsy results.	Relationships between fecal fat, D-xylose and biopsy results were not reported. While 38% of controls had PD, results for the markers studied were not stratified by PD for this group. Seven children with biopsies consistent with CD did not respond to gluten-free diet and were excluded from the study. Cut-off points used to define abnormal D-xylose tests were not provided.

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2000 Quadro L et al. Retinol and retinol-binding protein: gut integrity and circulating immunoglobulins L:M as a marker of small intestinal permeability, and its correlation with serum retinol among mildly malnourished children	Goncalves Dias favela in Fortaleza, Brazil 1-9 yr olds with mild malnutrition selected from a large cohort of children from an urban slum. They were recruited at birth and followed longitudinally. 19 (63%) had some degree of vitamin A deficiency—all of these had mild deficiency, except for 2 with moderately low concentrations.	Cross-sectional n =30	<u>Urine Tests</u>: • Lactulose[63] • Mannitol • L:M	80% of subjects had abnormal L:M, defined as >=0.030. Serum retinol was: • Inversely correlated with L:M (r=0.46, p=0.012) • Directly correlated with mannitol (r=0.66, p<0.01) • Not correlated with lactulose (data not reported)	Children with low serum retinol had higher L:M, apparently mediated by mannitol excretion.	The L:M normal cutoff was defined lower than for most other L:M studies, as 0.030. The authors reference several studies regarding use of this cut point.

[63] Lactulose and mannitol results were expressed as % of dose administered.

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2004 Rabbani GH et al. Green banana and pectin improve small intestinal permeability and reduce fluid loss in Bangladeshi children with persistent diarrhea L:M as a marker of intestinal permeability among infants with PD who are treated with green banana, pectin, or rice diet	Dhaka, Bangladesh 5-12 mo old males admitted to the hospital of the International Centre for Diarrhoeal Disease Research with PD but without other concurrent illnesses.	RCT n=57; n=19 received green banana and rice n=17 received pectin and rice n=21 received rice alone (placebo)	<u>Urine Tests</u>: • Lactulose[64] • Mannitol • L:M	Mean L:M[65] (SD) by treatment group, pre- and post-treatment: • Banana: pre=0.50 (0.14), post=0.21 (0.12), p<0.01 • Pectin: pre=0.54 (0.17), post=0.23 (0.09), p<0.01 • Placebo: pre=0.41 (0.11), post=0.45 (0.13), p>0.6 Lactulose and mannitol excretion did not differ between groups at baseline. Lactulose excretion was not significantly reduced after intervention in the placebo group. Mean (SD): • Pre-treatment: 1.45 (0.12) • Post-treatment: 1.35 (0.15) Both treatment groups had 70-80% reduced lactulose excretion following treatment (p<0.01). Mannitol excretion increased in all groups compared to their pre-treatment values, but only significantly so in the banana and pectin groups (p<0.05). Mean mannitol % excretion (SD), pre- vs. post-treatment: • Banana: 1.82 (0.13) vs.	L:M values were high at baseline among the study population of inpatient young children with PD. Mean L:M significantly improved with the green banana or pectin intervention but were still above normal range following 7 days of treatment. The improvements in L:M were driven by both mannitol and lactulose, with the latter having an impact of greater magnitude. Authors cite studies postulating that the effectiveness of green banana in reducing diarrheal fluid loss is due to its high content of amylase-resistant starch, which undergoes bacterial fermentation into	

[64] Lactulose and mannitol results were expressed as % of dose administered.
[65] Type of mean not specified.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				3.21 (0.16) • Pectin: 1.91 (0.12) vs. 3.2 (0.18) • Placebo: 2.10 (0.11) vs. 2.33 (0.18) The banana and pectin groups stopped having diarrhea more often compared to controls (e.g. $p<0.01$ by day 4). Among the banana and pectin groups, stool reductions were associated with percent change in L:M before and after treatment (R^2=0.84 for pectin and R^2=0.86 for banana; $p<0.05$ for each).	short-chain fatty acids in the colon, stimulating colonic salt and water absorption. Pectin is thought to work by a similar mechanism. Authors also suggest that short chain fatty acids might affect entero-hormones and growth factors, resulting in the observed changes in intestinal permeability [206].	
2001 Rabbani GH et al. Increased nitrite and nitrate concentrations in sera and urine of patients with cholera or shigellosis To assess and compare nitric oxide as a marker of intestinal inflammation among children with cholera	Dhaka, Bangladesh 2-6 yr olds with cholera or shigellosis admitted to the hospital. Controls were recruited from the healthy attendants of patients or from children of hospital staff. Mean age (SD) in	Case-control n=63; n=45 cases: • 24 with cholera • 21 with shigellosis n=18 healthy controls Samples were collected from cases on admission	<u>Urine Test</u>: Nitric Oxide (NO)* <u>Blood Tests</u>: • Nitrite (NO_2) • Nitrate (NO_3) • WBC <u>Stool Test</u>: Leukocytes * Nitric oxide (NO) is an unstable free radical that is	In children with shigellosis, median serum NO was ~8x higher at baseline than in controls and significantly differed from convalescent concentrations ($p<0.01$). Concentrations declined by 52% of baseline during the recovery period but did not return to values found in the controls (measure of statistical significance not reported). In children with cholera, median serum NO concentrations at baseline	NO as measured by both serum and urinary NO_2 and NO_3 concentrations was significantly elevated at presentation during acute illness compared to 7-10 days after hospitalization in both cholera and shigellosis. Median serum NO concentrations in	Some values reported in table format conflict with the text; columns of data appear to be transposed. Assessment for NO correlation with fecal leukocyte counts was not reported, nor was the correlation between urinary NO and total blood WBC.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
or shigellosis or healthy controls. Evaluated to assess nitric oxide production during infection of small bowel without inflammatory lesion (e.g., cholera) and during infection causing colon inflammation (e.g., shigellosis).	yr: • Shigellosis cases: 3.8 (1.2) • Cholera cases: 4.2 (1.4) • Controls: 4.7 (1.8)	and upon discharge (after 7-10 days of treatment).	converted to nitrite and nitrate. Urine NO_2 + NO_3 were expressed as a ratio with urine creatinine in order to account for differences in urine concentration.	were ~4x higher than in control subjects. Recovery concentrations decreased 52% from baseline ($p<0.01$); convalescent values did not differ from the values in controls ($p<0.4$). Median urinary NO ratios were similar among those with *Shigella* and *V. cholerae* infection, both upon admission and discharge. Initial values were ~2x higher than upon discharge ($p<0.05$ and 0.01, respectively). Control median NO was of an intermediate concentration between cases' admission and discharge median concentrations; the difference between control and case admission values was NS. Mean blood WBC counts (SD): • Shigellosis: 19.6 (3.3) • Cholera: 8.3 (2.8) • Controls: 7.1 (1.8) Mean fecal WBC/high power field (SD): • Shigellosis: 38 (17) • Cholera: 5 (2) • Controls: 3 (1) Serum NO correlated with blood WBC count in shigellosis cases at baseline ($r^2=0.92$, $p<0.01$), but only	cholera patients were ~half of those with shigellosis both upon admission and upon discharge and concentrations were much higher in cases than in controls, Such striking differences were not observed for urinary NO results. Serum NO concentrations correlated with total blood WBC in shigellosis cases.	

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				to a slight degree upon discharge (r^2=0.26, no p-value reported) and there was no correlation among the cholera cases. Serum NO correlated with stool volume at presentation (r^2=0.85, statistically significant per authors, p-value not reported).		
2009 Ritchie BK et al. 13C-sucrose breath test: novel use of a noninvasive biomarker of environmental gut health Sucrose breath test (SBT) as a marker of small bowel mucosal damage vis a vis sucrase activity among an Australian Aboriginal population. Also compared SBT with serum lactulose:rhamnose ratio (L:R)	Darwin and Adelaide, Australia 4 mo-5 yr old Aboriginal children admitted to hospital with diarrhea. Two control groups: 1. Aboriginal controls admitted to hospital with non-GI symptoms (50% had pneumonia) 2. Healthy, non-Aboriginal controls recruited from community	Case-control n=43; n=18 Aboriginal cases with AD n=25 controls: • 18 Aboriginal, without diarrhea • 7 non-Aboriginal, healthy	<u>Blood Tests</u>: • L:R (32 Aboriginal cases and controls tested) • C-reactive protein (CRP) • Mean Corpuscular Volume (MCV) • Hemoglobin <u>Breath Test</u>: ^{13}C sucrose breath test (SBT)	20/32 (63%) of Aboriginal children had abnormal L:R ratios. Mean[66] L:R (CI): • Diarrhea cases: 31.8 (24.9, 40.7) • Aboriginal controls without diarrhea: 11.4 (8.5, 15.5), significant difference (p<0.0001) SBT Mean (CI): • Diarrhea cases: 1.9% (0.9, 3.0), p<0.0001 compared to non-Aboriginal controls and p=0.004 compared to Aboriginal controls • Aboriginal controls: 4.1% (3.0, 5.2), p=0.032 compared to non-Aboriginal controls • Non-Aboriginal controls: 6.1% (4.8, 7.3) Significant differences were observed between all three groups.	SBT values were significantly lower and L:R values were significantly higher among Aboriginal children with diarrhea than among those without GI symptoms. SBT was also significantly lower among Aboriginal controls than among non-Aboriginal children without diarrhea. This is consistent with previous reports of high prevalence of clinically silent TE in this population. SBT was significantly inversely	Abnormal L:R ratios were defined as >16; no reference or derivation was provided for this cut-point. L:R test was not conducted among the non-Aboriginal controls. SBT/L:R correlation analysis was based on data for Aboriginal cases and controls combined; stratified analysis was not reported and could be of interest considering the large difference in L:R observed between these groups. Associations of

[66] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

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				SBT results were not associated with wasting or with patient age or breastfeeding status. SBT and L:R were inversely correlated (r=0.67; CI: 0.42, 0.62; p<0.0001). L:R explained 45% of the variance in SBT; diarrhea explained 28% of variance. SBT was associated with increased MCV, relative risk (CI)=3.9 (2.8, 5.0). SBT was not associated with hemoglobin or CRP.	correlated with L:R.	MCV, CRP, and hemoglobin with SBT after adjusting for potentially confounding variables were not reported.

2001
 	
Rollins NC et al.
 	
Feeding mode, intestinal permeability, and neopterin excretion: A longitudinal study in infants of HIV-infected South African women
 	
L:M as a marker of gut mucosal integrity and urinary neopterin excretion as a marker of cell-mediated immunity in infants with and
	Durban, South Africa
	
	1, 6, and 14 wk old infants born to HIV-infected mothers.
		Cohort
		
		n=272
			<u>Urine Tests</u>:
			• Lactulose[67]
			• Mannitol
			• L:M
			• Neopterin
				Mean[68] L:M (CI):
				• HIV-infected subjects:
				  • 1 wk: 0.12 (0.06, 0.27)
				  • 6 wk: 0.24 (0.15, 0.38)
				  • 14 wk: 0.24 (0.14, 0.44)
				• Uninfected subjects:
				  • 1 wk: 0.13 (0.09, 0.19)
				  • 6 wk: 0.08 (0.06, 0.11)
				  • 14 wk: 0.09 (0.07, 0.13)
				
				HIV-infection by 14 wk of age was significantly associated with increased L:M.
				
				A non-significant, positive trend in neopterin excretion was observed among HIV-
					L:M was generally normal (compared to UK values) for non-HIV-infected infants, but significantly increased among HIV-infected subjects, especially after 6 weeks.
					
					The increased L:M in HIV-infected infants was primarily driven by lactulose rather than mannitol.
						Assessment of association between L:M and neopterin was not reported.

[67] Lactulose and mannitol results were expressed in mg.
[68] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
without HIV infection				infected infants.	Higher neopterin excretion by HIV-infected infants was observed but this was not statistically significant.	

2000
 	
Rollins NC et al.
 	
Vitamin A supplementation of South African children with diarrhea: optimum timing for improving biochemical and clinical recovery and subsequent vitamin A status
 	
L:M as a marker of intestinal permeability and urinary neopterin, serum α-1 acid glycoprotein, and C-reactive protein as markers of inflammation among children with severe diarrhea
	Durban, South Africa
	
	6-60 mo old inpatients or outpatients with severe diarrhea.
		RCT
		
		n=139;
		
		n=66 received vitamin A on admission (group 1)
		
		n=73 received vitamin A after clinical improvement (group 2)
		
		Treatment involved vitamin A supplementation either on the day of admission or after acute diarrheal symptoms had resolved.
			<u>Urine Tests</u>:
			• Lactulose[69]
			• Mannitol
			• L:M
			• Neopterin
			
			<u>Blood Tests</u>:
			• C-reactive protein (CRP)
			• α-1 acid glycoprotein (AGP)
			
			49 subjects received urine testing:
			• Group 1: n=25
			• Group 2: n=24
			
			Blood and urine were tested on days 0 and 3.
				Mean[70] L:M:
				• Group 1:
				  • Day 0: ~1.8
				  • Day 3: ~2.4
				• Group 2:
				  • Day 0: ~1.2
				  • Day 3: ~0.7
				
				There were no differences in mean L:M between groups or within groups between days 0 and 3, although there was a significant difference in paired analysis within individuals at the two time points (data not presented, and direction, magnitude and degree of significance not reported).
				
				Lactulose and mannitol excretion were assessed only in the paired analysis. Lactulose excretion decreased between days 0 and 3 (magnitude of effect and degree of significance not reported), while mannitol excretion showed no change.
					Mean L:M ratios were very high (~10x) (at baseline and at day 3 in both groups) compared to other studies in this review. Study authors suggested (via personal correspondence) that this could have been due to the severity of illness in the sample population (children hospitalized for diarrhea).
					
					Vitamin A administration did not result in significant improvement in L:M, neopterin, or AGP regardless of timing of vitamin A administration.
						Urine testing could only be conducted in the laboratory on certain days; hence only a subset of subjects underwent those tests.
						
						Group 2 patients had significantly higher CRP, non-significantly higher WBCs and AGP, and lower retinol and retinol-binding protein concentration compared to group 1 at baseline. Authors note that these parameters suggest that Group 2 patients might have been more ill at baseline. For the subset of 49 patients undergoing urine testing, the mean[72] L:M and neopterin concentrations

[69] For lactulose, mannitol, and neopterin results, excretion measurement was not specified.
[70] Geometric mean.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				Mean[71] neopterin and AGP concentrations did not differ between groups or within groups on the different study days or in the paired analysis. When initial CRP (~2x higher in Group 2 compared to Group 1, p<0.004) was taken into account, mean CRP on day 3 did not differ between the 2 groups. However in the paired analysis, CRP concentrations were significantly different between days 0 and 3.		were lower among Group 2 than Group 1 subjects (NS). However, baseline differences in acute phase and vitamin A markers at baseline were not reported separately for these 49 subjects. Data for lactulose and mannitol excretion were not reported separately. Rationale for additional analyses of these molecules expressed as ratios with creatinine was not explained. Authors suggest that their 3-day testing period (based on their previous work in a different setting [207] might have been too short to identify effect as demonstrated by McCullough et al. at 10 days after presentation [208].

[72] Geometric mean.
[71] Geometric mean.

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2006 Samie A et al. *Cryptosporidium* species: preliminary descriptions of the prevalence and genotype distribution among school children and hospital patients in the Venda region, Limpopo Province, South Africa Stool lactoferrin as a marker of intestinal inflammation among hospitalized patients and school children	Vhembe, South Africa 0.1-88 yr olds from semi-urban community included patients hospitalized with diarrhea or other GI complaints as well as students attending nearby schools.	Cross-sectional n=26 ≤5 yr old: • 22 hospital-based subjects • 4 school-based subjects	Stool Test: Lactoferrin	16/22 patients and 0/4 students were lactoferrin positive. While examination of lactoferrin association with history of diarrhea or with *Cryptosporidium* infection was not reported, only 3/22 and 16/22 hospitalized patients and 2/4 and 3/4 school children were positive for *Cryptosporidium* and had a history of diarrhea, respectively.	Lactoferrin prevalence was high among children hospitalized with diarrhea or other GI symptoms, regardless of *Cryptosporidium* status. Lactoferrin was not found among school-recruited children, most of whom did have a history of diarrhea. Two of the four school children were *Cryptosporidium*-positive.	Among the entire study cohort of all ages, lactoferrin results were similar among hospitalized patients regardless of *Cryptosporidium* status (influence of HIV infection was not reported). Among school children, lactoferrin was more frequently found to be positive among those infected with *Cryptosporidium;* statistical testing was not reported. Lactoferrin results were graded based on agglutination reaction positivity with increasing dilution and was considered negative if there was no reaction at 1:25. Some subjects were breastfed and were tested for lactoferrin.
2004 Sarker SA et al.	Dhaka, Bangladesh 2-5 yr old	Case-control n=25:	Blood Test: Iron (absorption test)	Mean[73] iron absorption from ferrous (Fe) sulfate and Fe fumarate: • Uninfected children:	Iron absorption from Fe fumarate was significantly lower than from	Data on iron absorption among 2-5 yr olds are limited, making

[73] Geometric mean.

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Helicobacter pylori infection, iron absorption, and gastric acid secretion in Bangladeshi children Iron absorption among children with iron deficiency anemia with and without *H. pylori* infection	apparently healthy children from a periurban setting, screened for iron deficiency and *H. pylori*.	n=13 cases infected with *H. pylori* n=12 controls not infected with *H. pylori*		15.6% and 5.4%, (p<0.001) • Infected children before treatment: 19.7% and 5.3%, (p<0.0001) • Infected children after treatment: 22.5% and 6.4%, (p<0.0001) • *H. pylori* treatment did not significantly affect absorption (Fe sulfate or fumarate), p=0.3	Fe sulfate. Results do not support the hypothesis that *H. pylori* infection influences absorption of water-soluble (Fe sulfate) or non-water-soluble (Fe fumarate) iron compounds.	comparison of results from this study setting difficult.
2006 Sheng XY et al. Major variables of zinc homeostasis in Chinese toddlers Differences in zinc absorption in healthy toddlers with a high prevalence of zinc deficiency.	Xi-Chou (town) & Yun-Nan (province), China 19-25 mo olds recruited from a remote small town and 2 surrounding rural villages. 48% of children had plasma zinc concentrations below 2.5th percentile. Dietary zinc intake was low. There was a high prevalence of stunting among the subjects.	Cross-sectional n=43	<u>Stool Test</u>: Endogenous fecal zinc (EFZ) <u>Urine Test</u>: Zinc excretion to measure fractional absorption of zinc (FAZ) and total absorbed zinc (TAZ) following radiolabeled zinc administration	Mean (SD): • FAZ: 0.35 (0.12) • AZ (mg/d): 0.63 (0.24) • EFZ (mg/d): 0.67 (0.23) The quantity of absorbed zinc was lower than physiologic requirements. There was no statistically significant difference in any laboratory value between the town and village groups. Zinc absorption was ~80% of estimated physiologic requirement and equivalent to the amount of endogenous zinc excreted via the intestine; it was expected that absorbed zinc would exceed excreted zinc [144, 187, 194, 195].	Zinc absorption was lower than physiologic requirements and EFZ was higher than expected. The authors note that the results are difficult to explain and specifically state that they do not think (though without clear justification) that enteropathy is prevalent in the population and therefore could not be a contributing factor.	
2008 Sherwani K et al.	Aligarh, India 1-12 yr olds (mean age 51.2 mo) from	Cross-sectional n=19	<u>Duodenal biopsy, method not specified:</u> Histopathology	Six patients had partial villous atrophy and non-specific duodenitis by biopsy.	Biopsy identified abnormal histopathology in approximately 1/3	The 6 children with partial villous atrophy were thought to have

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Prevalence of iron deficiency anemia in chronic diarrhoea and celiac disease - A western UP experience Duodenal biopsy in patients with PD	an urban setting with PD recruited from pediatric outpatient and inpatient units. Those with negative CD work-up were subjects of interest for this review.				of patients who did not have CD, but did not identify PD etiology in the remainder who did not have CD.	SBBO as they recovered after treatment with broad spectrum antibiotics.

2003
 	
Soliman SM et al.
 	
Role of micronutrient mixture in acute and persistent diarrhea in infants and its impact on nutritional status
 	
Blood cell and albumin markers among infants with acute, persistent or no diarrhea, and effects on these markers after 10 days of supplementation with micronutrient mixture (containing vitamin A, zinc and other micronutrients) among subjects with and without diarrhea
	Cairo, Egypt
	
	6-24 mo olds with diarrhea were recruited from Al-Sahel teaching hospital malnutrition clinic.
	
	5/6 PD cases and 10/14 AD cases had some degree of malnutrition.
	
	Infants with PD had significantly lower vitamin A and zinc stores compared to controls. Those with AD had significantly lower vitamin A stores.
		Case-control
		
		n=30;
		
		n=20 cases:
		• 6 with PD
		• 14 with AD
		
		n=10 healthy controls*
		
		* Controls were age- and sex-matched to cases.
			<u>Blood Tests</u>:
			• Complete blood count and differential
			• Red cell measures:
			  • Mean corpuscular volume (MCV)
			  • Mean corpuscular hemoglobin (MCH)
			  • Mean corpuscular hemoglobin concentration (MCHC)
			  • Transferrin saturation
			• Albumin
				Mean baseline hemoglobin was significantly lower in infants with AD and PD ($p<0.05$ for each group) than in controls
				
				Mean MCV and MCH were lower in those with AD ($p<0.025$ and $p<0.01$, respectively) and PD ($p<0.01$ for both markers) compared to controls.
				
				Mean lymphocyte counts among PD cases were low compared to those of controls ($p<0.01$).
				
				Other markers did not vary significantly at baseline. However, among infants with PD, mean albumin was abnormally low, although it was not significantly different compared to controls or those with AD.
				Mean albumin (g/dL) (SE):
				• PD: 2.9 (0.27)
				• AD: 3.29 (0.25)
				• Controls: 3.37 (0.21)
					Albumin and many hematologic markers were low at baseline among infants with diarrhea, especially in those with PD, compared to those without diarrhea; some of these differences were statistically significant. Parameters generally normalized after micronutrient supplementation.	Information on control recruitment and anthropometrics were not specified.
						
						Sample size was small when stratified by case/control groups, especially for PD cases (n=6). Controls were reported to have been matched to cases, yet there were half the number of controls than cases and statistical testing (student's t-test) was not commensurate with matched case-control methodology.

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				Following micronutrient supplementation, mean hemoglobin, MCV, lymphocyte counts and albumin increased in both diarrhea groups to concentrations on par with control baseline concentrations (albeit increases were NS except within the PD group). MCH improved to concentrations on par with the control group only among the infants with AD.		
2003 Tassara O et al. Gastrointestinal diseases in children infected with the human immunodeficiency virus Endoscopy and biopsy among HIV-infected children	Santiago, Chile 0-12 yr old (median 9 mo) HIV-infected children treated in hospital. A high proportion had PD.	Cross-sectional n=11	<u>Endoscopic upper GI biopsy</u> including esophagus, stomach, and/or duodenum: • Gross endoscopic visualization • Histopathology	Macroscopic inflammatory changes were observed on endoscopy in the esophagus, stomach or duodenum in 2 subjects. Biopsies of esophagus, stomach or duodenum showed inflammatory changes of varying degree in all 11 subjects.	Biopsy results might show inflammatory damage in cases with no macroscopic damage visible.	Spanish language article. Inflammatory changes identified in the digestive system were not specified by site (i.e. esophagus, stomach or duodenum). Results were not stratified by presenting symptoms, including PD.
2000 Thurnham DI et al. Innate immunity, gut integrity, and vitamin A in Gambian and Indian	Orissa State, India Subjects were recruited from 2 sources: 1. Hospital-based infants admitted for “diarrheal or	RCT n=174; n=94 hospital-based • 31 received vitamin A at day	<u>Urine Test</u>: L:M For hospital-based subjects, L:M was assessed at baseline, discharge from	Mean L:M was ~3-fold higher among hospitalized compared to clinic patients at baseline. Within the allocation groups, mean baseline L:M did not differ for either the hospitalized or clinic subjects.	Mean L:M values, including post-intervention values, were 2-5 times higher than those observed in the UK [209].	Precise numerical values were not reported, rather L:M results were portrayed in figures with units expressed in mg, making it difficult to

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infants L:M as a marker of intestinal integrity among children receiving vitamin A supplementation	respiratory disease," mean age 9 mo 2. Clinic-based infants with "minor ailments", age not specified	1 • 32 received vitamin A at discharge (up to day 5) • 31 received placebo n=80 clinic-based* Clinic-based subjects were randomized to receive vitamin A weekly for 8 wk or placebo. * Number of subjects in each treatment group was not specified.	hospital, and 10 or 30 days after discharge. For clinic-based subjects, L:M was assessed at baseline, 4, and 8 wk.	Among the hospital cohort, mean L:M declined significantly in the two vitamin A groups compared to the placebo group, and remained lower at day 30 among the treatment groups, but the difference was no longer significant compared to the placebo group. Among the clinic cohort, mean L:M reduction was accelerated in vitamin A-supplemented children. However, mean L:M did not significantly differ between treatment groups at any time point. The rate of decline in L:M was most steep among the vitamin A-treated hospitalized patients, in whom the mean L:M value decreased by 63% over 30 days, followed by placebo-treated hospitalized patients, with a decrease of 38% over 30 days. Mean L:M decreased by 57% in the vitamin A-treated clinic patients, while there was no change in L:M among the clinic placebo group.	L:M reduction was accelerated among vitamin A-supplemented children, but end-of-study mean values did not differ statistically between allocation groups in either the clinic or the hospital cohorts.	compare these results to those of other studies. Information on study design, such as randomization scheme, was limited. The article also reported re-analyzed data from a 1991 report from The Gambia [209].

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2009
 	
Trehan I et al.
 	
A randomized, double-blind, placebo-controlled trial of rifaximin, a nonabsorbable antibiotic, in the treatment of tropical enteropathy
 	
L:M, sucrose:lactulose, and sucralose:lactulose as markers of small intestinal, gastric, and colonic permeability, respectively, among those receiving rifaximin or placebo
	Limela, Malawi
	
	All 3-5 yr olds from the village were recruited.
		RCT
		
		n=144;
		
		n=72 received rifaximin for 7 days
		
		n=72 received placebo
		
		It was presumed that if SBBO is the etiology for enteropathy, treatment with rifaximin would result in improved intestinal integrity.
			<u>Urine Tests</u>
			• Lactulose[74]
			• Mannitol
			• Sucrose (SUC)
			• Sucralose (SCL)
			• L:M
			• Sucrose:lactulose ratio (SUC:L)
			• Sucralose:lactulose ratio (SCL:L)
			
			Subjects were tested before and after treatment.
				At enrollment:
				• Mean mannitol (SD):
				  • Treatment: 9.57 (5.24)
				  • Placebo: 10.29 (6.62)
				• Mean lactulose (SD):
				  • Treatment: 0.30 (0.18)
				  • Placebo: 0.34 (0.25)
				• Mean SUC (SD):
				  • Treatment: 0.062 (0.04)
				  • Placebo: 0.074 (0.058)
				• Mean SCL (SD):
				  • Treatment: 0.51 (0.29)
				  • Placebo: 0.58 (0.53)
				• Mean L:M[75] (SD):
				  • Treatment: 0.18 (0.12)
				  • Placebo: 0.17 (0.09)
				• Mean SUC:L (SD):
				  • Treatment: 0.50 (0.34)
				  • Placebo: 0.64 (0.90)
				• Mean SCL:L (SD):
				  • Treatment: 0.42 (0.32)
				  • Placebo: 0.39 (0.23)
				• For both groups combined:
				  • 76% had L:M >0.10
				  • 34% had L:M >0.20
				
				No significant post-intervention differences were observed in any fractional sugar excretion or dual sugar test, including among children with elevated pre-intervention L:M.
					There was a high proportion with elevated L:M which did not change with rifaximin treatment.
					
					Baseline L:M measurements in this study resembled those of another Malawian population in similar environmental conditions [120].
					
					SCL excretion in this population was similar to that found in healthy American children (0.4%), while SCL:L was comparatively lower (0.8) and driven by lactulose [210]. SCL:L might be a better marker of colonic permeability [211-213]. Results from this study potentially indicate that colonic
						Methodological differences in specimen collection and testing, in particular for SCL excretion, might account for some differences in values compared to other studies.
						
						This was the first use of SCL for site-specific absorption testing in a developing country setting.

[74] Lactulose, mannitol, SUC, and SCL results were expressed as % of dose administered.
[75] Type of mean for sugar ratios not specified.

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					permeability was normal. Few data exist on SUC excretion. Results in this trial are similar to those found in another Malawian population (0.06% SUC excretion) [120] and high compared to healthy older children from developed country settings (0.02-0.03%) [210, 212].	
2008 Vieira MM et al. Carotenoids, retinol, and intestinal barrier function in children from northeastern Brazil L:M as marker of intestinal barrier function, fecal lactoferrin and leukocytes as markers of intestinal inflammation, and CRP and AGP as acute phase reactants among	Fortaleza, Brazil 2 mo-9 yr olds (mean age 41 mo) from an impoverished urban community, eligible if HAZ score <median for their community.	Cross-sectional n=102	<u>Urine Tests</u>: • Lactulose[76] • Mannitol • L:M (97 tested) <u>Stool Tests</u>: • Lactoferrin (93 tested) • Leukocytes <u>Blood Tests</u>: • C-reactive protein (CRP) • α-1-acid glycoprotein (AGP)	48.5% had abnormal L:M. L:M and excretion of each sugar separately did not vary with retinol concentration. L:M was associated with levels of common dietary carotenoids, primarily driven by lactulose. However, the association was not always statistically significant, and the direction of association varied depending on precursor. 40% of stool samples were positive for lactoferrin.	Almost half of subjects had increased L:M, and ~40% of subjects had increased lactoferrin. While serum retinol concentrations were not associated with L:M, serum carotenoids were; authors suggest that these retinol precursors might be more sensitive predictors of	L:M threshold for abnormal values was defined as <u>≥</u>0.0864 [214]. Cut-off values for lactoferrin positivity were not described. Relationships between acute phase proteins and measures of intestinal permeability or inflammation were not reported. Relationships between L:M and lactoferrin or fecal

[76] Lactulose and mannitol results were expressed as % of dose administered.

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
children with varying vitamin A status				1% of stool samples were positive for fecal leukocytes. 30% of stool samples were positive for parasites but this had no impact on L:M results, lactoferrin, or acute phase reactants.	impaired intestinal function. However, the reported direction of association varied, making interpretation of these results unclear.	leukocytes as well as those between retinol or carotenoids and lactoferrin or fecal leukocytes were not reported. Exclusively breastfed children were excluded from study participation due to assessment of stool lactoferrin.

2007
 	
Williams EA et al.
 	
A double-blind, placebo-controlled, glutamine-supplementation trial in growth-faltering Gambian infants
 	
L:M and plasma immunoglobulins and acute phase reactant proteins (albumin, C-reactive protein, and alpha-1-antichymotrypsin) in community-based Gambian infants enrolled in a glutamine trial
	West Kiang region, Gambia
	
	4-10 mo olds from a rural area followed during the 5-month rainy season and for 6 months afterward.
		Cohort
		
		n=72
		
		Glutamine or placebo of nonessential amino acids was orally administered twice daily during rainy season; L:M ratio was measured monthly, and plasma samples were collected 3 times.
			<u>Urine Tests</u>:
			• Lactulose[76]
			• Mannitol
			• L:M
			
			<u>Blood markers</u>
			• C-reactive protein (CRP)
			• Alpha-1 antichymotrypsin (ACT)
			• IgA
			• IgG
			• IgM
			• Albumin
				Mean[77] L:M (CI):
				• Baseline:
				  • Glutamine group: 0.33 (0.25, 0.43)
				  • Placebo group: 0.33 (0.26, 0.41)
				• Post-intervention:
				  • Glutamine group: 0.29 (0.23, 0.35)
				  • Placebo group: 0.26 (0.21, 0.32)
				
				Mean excretion of lactulose (CI):
				• Baseline:
				  • Glutamine group: 0.21 (0.16, 0.28)
				  • Placebo group: 0.20 (0.15, 0.26)
				• Post-intervention:
				  • Glutamine group: 0.17 (0.13, 0.21)
				  • Placebo group: 0.14
					L:M values were elevated in this population, with no significant change after the intervention.
					
					None of the plasma markers differed significantly between treatment and placebo groups, either at baseline or at the end of supplementation.
					
					Growth outcomes did not differ significantly across treatment groups.
						The relationships between L:M and growth parameters, immuno-globulins, and acute phase proteins were not reported.

[77] Geometric mean

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments

				(0.11, 0.18)
				
				Mean excretion of mannitol (CI):
				• Baseline:
				  • Glutamine group: 2.65 (2.02, 3.48)
				  • Placebo group: 2.50 (1.87, 3.36)
				• Post-intervention:
				  • Glutamine group: 2.48 (1.99, 3.11)
				  • Placebo group: 2.14 (1.62, 2.82)
				
				L:M values did not differ significantly between treatment groups before or following intervention. However, a repeated measures ANOVA showed that during supplementation, L:M values were borderline elevated among the glutamine-supplemented group relative to the placebo group (p=0.05), counter to expectation.
				
				Neither ACT, CRP, albumin, nor immunoglobulins IgA, IgG, or IgM differed significantly between treatment and placebo groups, either at baseline or at the end of supplementation.
				
				Mean levels of IgA and IgG increased during the study (p <0.001), while IgM levels		

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				did not. Concentrations of each of these immunoglobulins did not differ between treatment and placebo groups. Plasma albumin, ACT, and CRP values showed no change over the course of the study. Proportions of children with elevated CRP ranged from 30-41% at different collection time points. The glutamine intervention had no effect on proportion of children with elevated CRP. Treatment and placebo groups experienced decreases in WAZ, HAZ, and MUAC coinciding with the rainy season; however, there was no significant difference observed between the groups for any of these parameters. Treatment and placebo groups did not differ in morbidity indices (i.e. percentage of time reported with a particular illness or illness overall).		
2000 Willumsen JF et al. Subclinical mastitis as a risk factor for	Durban, South Africa HIV-infected breastfeeding mothers and their	Cross-sectional analysis of baseline data prior to randomization for an RCT	<u>Urine Test:</u> L:M	There was no significant association between L:M and subclinical mastitis as measured by milk Na/K.	Subclinical mastitis was not associated with magnitude of L:M.	Actual L:M values were not reported but are found in a companion study, also included in this review [119].

Appendix 7. Evidence table of all studies included in the review.

Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
mother-infant HIV transmission L:M as a marker of infant intestinal permeability and its relationship with subclinical maternal mastitis	infants followed up to 14 wk of age. Women recruited from antenatal clinic via a vitamin A supplementation trial to reduce mother-to-child HIV transmission.	n=104 mothers n=108 infants (4 pairs of twins), (26 were HIV-infected by 3 mo of age)				The study group in Willumsen, et al. represents a subsample of the study population reported in the companion study.
2000 Zhang Y et al. Lactulose-mannitol intestinal permeability test in children with diarrhea caused by rotavirus and *Cryptosporidium* L:M as a marker of intestinal permeability in children with diarrhea	Lima, Peru 0-36 mo olds with watery diarrhea admitted to oral rehydration unit of hospital.	Case-control n=36; n=29 cases: • 15 with *C. parvum* alone • 7 with rotavirus alone • 7 with bacteria (alone or with rotavirus or *Cryptosporidium*) n=7 controls with unknown etiology	<u>Urine Test</u>: L:M Enrollment and convalescent (at day 20) L:M ratios were assessed.	Mean[78] L:M (SE) at day 1, day 20: • Rotavirus only: 0.67 (0.38), 0.19 (0.09) • Cryptosporidium only: 0.76 (0.43), 0.28 (0.14) • Bacterial infection: ranged from 0.2-0.87, 0.11-0.99 • Unknown etiology: 0.26 (0.12), 0.29 (0.18) Mean L:M ratios significantly differed between the unknown etiology and both the rotavirus ($p< 0.01$) and *Cryptosporidium* groups ($p<0.05$) at baseline, but not at day 20. Mean L:M ratios decreased between baseline and day 20 for both the rotavirus ($p<0.001$) and *Cryptosporidium* ($p<0.05$) groups. Among the group of subjects with enteric bacterial infections, the	L:M ratios were significantly elevated in children with rotavirus or *Cryptosporidium* infection compared to those with diarrhea not caused by rotavirus, *Cryptosporidium*, or identifiable bacteria. Mean L:M did not change significantly among those with diarrhea of unknown etiology, but did significantly decrease among those infected with rotavirus or *Cryptosporidium*, reaching ratios	

[78] Arithmetic mean.

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Reference and Study Outcomes of Diagnostic Interest	Location and Target Population	Design and Sample Size	Biomarker	Results	Conclusion	Comments
				causative agents identified and mean L:M ratios (baseline, day 20) were: *Campylobacter jejuni* and rotavirus infection (0.86, 0.18), *C. jejuni* and *Cryptosporidium* infection (0.87, 0.53), *Salmonella* sp. (0.2, 0.11), *C. jejuni* (0.69, 0.99), and *Aeromonas* sp. (0.38, 0.11). The L:M ratios of this group of seven infants were not included in the statistical analyses.	similar to those with diarrhea of unknown etiology.	

Notes: Some studies included subjects ≥5 yr of age. Where these studies provided data separately for children <5 yr, we present results for only those subjects. Where these studies did not stratify results by age, but did report the number of children <5 yr included in the study, we provide a breakdown of under-5s.
All studies reporting lactulose:rhamnose ratio results presented values multiplied by a factor of 100 for ease of reporting.
Further details on L:M studies can be found in Table 14.

Abbreviations: AD=acute diarrhea, ALT=alanine aminotransferase, AST=aspartate aminotransferase, CBC=complete blood count, CD=celiac disease, CI=95% confidence interval, Cr=creatinine, Δ=change in, EED=environmental enteric dysfunction, FTT=failure to thrive, GI=gastrointestinal, HAZ=height-for-age Z-(score), HDL=high density lipoproteins, HIV=human immunodeficiency virus, HLA=human leukocyte antigen, IEL=intraepithelial lymphocytes, IgA=immunoglobulin A, IgE=immunoglobulin E, IgG=immunoglobulin G, IgM=immunoglobulin M, IL=interleukin, IFN=interferon, LDL=low density lipoproteins, L:M=lactulose:mannitol ratio, mo=month(s), NS=not statistically significant, PD=persistent diarrhea, RCT=randomized controlled trial, SBBO=small bowel bacterial overgrowth, SD=standard deviation, SE=standard error, SES=socioeconomic status, Tc-99m=technetium 99, T3=triiodothyronine, T4 = thyroxine, TE=tropical enteropathy, TGF=transforming growth factor, TNF=tumor necrosis factor, TS=tropical sprue, WAZ=weight-for-age Z-(score), WBC=white blood cell count, WFA=weight-for-age, WHZ=weight-for-height Z-(score), wk=week(s), yr=year(s)