

1 **Epidemiology, detection, and intervention/control of**
2 ***Cyclospora cayetanensis*: A scoping review protocol**

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18 Publication date: February 4th, 2020

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20 **Abstract**

21 *Background:* Cyclosporiasis is a food- and waterborne illness in humans caused by the
22 consumption of contaminated food or water. As the causative agent, *Cyclospora cayetanensis*,
23 has only been recently described, the published literature is limited and no scoping reviews on
24 this topic have yet been conducted.

25 *Objectives:* Our objective is to conduct a scoping review of the epidemiology, detection in
26 matrix, and intervention/control of *C. cayetanensis* worldwide in humans, plant-based food, and
27 in the environment with the aim of identifying gaps in the literature, potential areas where there
28 may be sufficient literature to warrant a systematic review, and prioritizing future research
29 directions.

30 *Eligibility criteria:* All primary research, systematic reviews, scoping reviews and quantitative
31 risk assessments in English, conducted anywhere in the world on the epidemiology, detection in
32 matrix, and intervention/control of *Cyclospora cayetanensis* are eligible. Studies of the
33 pathogenesis, diagnosis of illness in people, and treatment of cyclosporiasis are not eligible.

34 *Sources of evidence:* The following databases will be searched: MEDLINE® (Web of
35 Science™), Agricola (ProQuest), CABI Global Health, and Food Science and Technology
36 Abstracts (EBSCOhost) from 1979 to the present.

37 *Charting methods:* We will extract information on general study characteristics, study purpose
38 (epidemiology, detection, control) and within each of these categories, the study setting, study
39 design, life cycle stage of *Cyclospora* investigated, and matrices tested. Based on the purpose of
40 the study we will also extract the method of detection evaluated, risk factors for human illness,
41 environmental and food contamination, incidence/prevalence in the environment and on food
42 types, or the control approaches investigated.

43 **1. Introduction**

44 *1.1. Rationale*

45 *Cyclospora cayetanensis* is a single-celled parasite that causes an illness called cyclosporiasis in
46 humans when a person consumes water or food contaminated with the organism (CDC, 2019). *C.*
47 *cayetanensis* is shed in the feces by infected people. After 1 to 2 weeks in the environment, the
48 organism reaches the life cycle stage (sporulated oocyst) that is infectious to other people (CDC,
49 2019). Although the disease most commonly occurs in tropical and subtropical regions, people in
50 all parts of the world may become infected via ingestion of contaminated fresh produce imported
51 from those regions, with a recent outbreak occurring in the USA in 2019 linked to basil from
52 Mexico (CDC, 2019).

53

54 Scoping reviews are a type of literature review used for knowledge synthesis (Munn et al., 2018;
55 Tricco et al., 2018). Scoping reviews use systematic and transparent methods to summarize
56 research on broad topics, map the available evidence, and identify gaps in the current knowledge
57 (Tricco et al., 2018). A scoping review may act as a prelude to a systematic review and/or it may
58 help direct the focus of future primary research by highlighting areas where no research has been
59 conducted (Munn et al., 2018).

60

61 *C. cayetanensis* was first reported in humans in 1979 (Ashford, 1979) but it was not fully
62 identified until the early 1990s (Ortega and Sanchez, 2010). The literature base on this organism
63 consequently appears to be relatively limited; preliminary searches for existing scoping reviews
64 and systematic reviews of *Cyclospora* were conducted on December 12th, 2019 in MEDLINE®
65 (Web of Science™) (dates searched: 1950-Present), Agricola (ProQuest) (dates searched: 1970-

66 Present), and CABI Global Health (dates searched: 1973-present) using the search terms
67 ["*Cyclospora*" AND "systematic review"] and ["*Cyclospora*" AND "scoping review"]. The same
68 search was conducted in Food Science and Technology Abstracts (EBSCOhost) on January 3rd
69 2020. No scoping or systematic reviews of *Cyclospora* were found.

70

71 *1.2. Objectives*

72 Our objective is to conduct a scoping review of the epidemiology, intervention/control, and
73 detection in matrix of *Cyclospora cayetanensis* worldwide in humans, plant-based food, and in
74 the growing environment, i.e. water and soil, with the aim of identifying research gaps in the
75 literature and prioritizing future research directions, and identifying topics with sufficient
76 evidence base for systematic reviews.

77

78 **2. Methods**

79 *2.1. Protocol and registration*

80 This protocol was drafted using the Preferred Reporting Items for Systematic Reviews and Meta-
81 Analyses Extension for Scoping Reviews (PRISMA-ScR) (Tricco et al., 2018). This protocol
82 will be registered on the University of Guelph Atrium and can be accessed at SYREAF
83 [www.syreaf.org].

84

85 *2.2. Eligibility criteria*

86 Studies included in the review must be:

87 1) published in English (though studies in English from any part of the world are eligible);

88 2) primary research, systematic reviews, scoping reviews, or quantitative risk assessments
89 (QRA) only. Narrative or non-systematic reviews will not be eligible for inclusion, as the
90 absence of reported methods precludes the assessment of rigor and comprehensiveness;
91 3) studies of *Cyclospora cayetanensis*, as this is the only species of *Cyclospora* that causes
92 cyclosporiasis in humans (CDC, 2019). Studies that report only *Cyclospora* species but do not
93 specify that the organism is *C. cayetanensis* will therefore not be eligible.; 4) studies of any life
94 stage (oocysts, sporocysts, or sporozoites) in any exposure source (soil, water and plants-based
95 food).
96 In humans, direct person-to-person transmission of cyclosporiasis does not occur (CDC, 2019)
97 therefore this is not of interest to the review. According to the CDC, animals have not been
98 documented as an intermediate or primary host of *C. cayetanensis* and therefore animal studies
99 are not of interest. Studies of the diagnosis of human illness, pathogenesis, and treatment of
100 cyclosporiasis are not eligible for this review.

101

102 2.3. Information sources

103 To identify relevant studies, the following databases will be searched from 1979 to the present:
104 MEDLINE® (Web of Science™), Agricola (ProQuest), CABI Global Health, and Food Science
105 and Technology Abstracts (EBSCOhost). As the focus of this scoping review is broad and the
106 topic is relatively new, we consider it appropriate to conduct a simple search (with no
107 restrictions on study design or research focus) that will not require specialized information
108 retrieval knowledge; therefore the review team designed the search without input from a library
109 scientist. Results of the database searches will be uploaded into Endnote® X8 Desktop for de-
110 duplication. The resulting de-duplicated results will be imported into DistillerSR® (Evidence

111 Partners, Ottawa, ON, Canada) review management software for further de-duplication. We will
 112 also scan the reference lists of ten (subject to availability) of the most recently published
 113 narrative reviews for additional relevant studies. We will not be contacting authors to identify
 114 additional studies.

115

116 *2.4. Search*

117 The search strategy for MEDLINE® is in Table 1, Agricola (ProQuest) is in Table 2, CABI
 118 Global Health is in Table 3, and for Food Science and Technology Abstracts (EBSCOhost) is in
 119 Table 4, and will be conducted by members of the review team (AOC and ST). Given the
 120 simplicity of the search string we did not submit the search strategy for peer review. There will
 121 be no document-type or language restrictions included in the search, but the search will be
 122 limited to studies published from 1979 to the date of the search, since *C. cayetanensis* was first
 123 reported in humans in this year (Ashford, 1979). We did evaluate the addition of a wildcard (*)
 124 term in the search (cyclospor*) however this was not included in the final search because it
 125 added tremendously to the search results but the majority of new citations were irrelevant studies
 126 on the antibiotic Cyclosporine A, a cyclic nonribosomal peptide, cyclosporin (a polypeptide).
 127 Adding the terms Title (TI), MeSH Heading or MESH Major Topic did not add identify any
 128 unique hits to the search

129

130 *Table 1: Proposed search strategy¹ in MEDLINE® (Web of Science™) for a scoping review of the epidemiology, detection, and*
 131 *intervention/control of Cyclospora cayetanensis.*

132

Search no.	Search string
1	TS=cyclospora Indexes=MEDLINE Timespan=1979-2020

2	TS=cyclosporiasis Indexes=MEDLINE Timespan=1979-2020
3	TS=cayetanensis Indexes=MEDLINE Timespan=1979-2020
4	#3 OR #2 OR #1

133 ¹ There will be no document type or language restrictions.

134

135 *Table 2: Proposed search strategy in Agricola (ProQuest) for a scoping review of the epidemiology, detection, and*
 136 *intervention/control of Cyclospora cayetanensis.*

Search no.	Search string
1	cyclospora OR cyclosporiasis OR cayetanensis

137 Search will be from January 1st, 1979 to present.

138 There will be no restrictions on source type, document type, or language.

139

140 *Table 3: Proposed search strategy in CABI Global Health for a scoping review of the epidemiology, detection, and*
 141 *intervention/control of Cyclospora cayetanensis.*

Search no.	Search string
1	(cyclospora) OR (cyclosporiasis) OR (cayetanensis) AND yr:[1979 TO 2020]

142 Search will be from 1979 to present with no document type restrictions. Search of "all fields."

143

144 *Table 4: Proposed search strategy in food science and technology abstracts*

Search no.	Search string
1	(cyclospora) OR (cyclosporiasis) OR (cayetanensis) AND yr:[1979 TO 2020]

145

146

147 *2.5. Selection of sources of evidence*

148 In DistillerSR®, two reviewers working independently will assess the retrieved records for
149 eligibility, first based on the title/abstract, then, if they are deemed likely to be relevant, on the
150 full text. For eligibility assessment based on the title/abstract, two reviewers will be required to
151 exclude any record. For eligibility assessment based on the full text, two reviewers will be
152 required to include or exclude any record. Conflicts will be resolved via discussion, and if
153 consensus cannot be reached, by consulting a third reviewer.

154

155 The title/abstract screening form was pre-tested by all reviewers on 100 records and revised as
156 needed for clarity and consistency, before screening begins. This form comprises the following
157 question:

158

159 Q1. Based on the title/abstract, is the study a systematic review, a scoping review, a
160 QRA, a computer model (in silico) study, a burden of illness study, a molecular
161 characterization study or primary
162 research on detection in matrix, epidemiology of the exposure source, epidemiology
163 of human exposure, and/or intervention/control of the exposure source in *Cyclospora*
164 *cayetanensis*?

165 a. Yes (proceed to full-text screening)

166 b. No (exclude)

167 c. Unclear (proceed to full-text screening)

168 d. No, but it may be a relevant narrative review (exclude)

169

170 The full-text screening form was pre-tested by all reviewers on five records and revised for
171 clarity and consistency prior to the beginning of screening. This form comprises the following
172 questions:

173

174 Q1. Is the full text available in English?

175 a. Yes (proceed to Q2)

176 b. No, the full text is not in English (exclude) Specify language _____

177 c. No, the full text is not available (exclude)

178 Q2. Does the full text describe a study on *Cyclospora cayetanensis*?

179 a. Yes (proceed to Q3)

180 b. No (The study is of a different species of *Cyclospora*) (exclude)

181 c. No (The study is not on *Cyclospora* at all) (exclude)

182 Q3. Does the full text describe primary research, a systematic review, a scoping review, a
183 computer model study, a burden of illness study or a QRA of *Cyclospora*
184 *cayetanensis*?

185 a. Yes (proceed to Q4)

186 b. No (exclude)

187 c. No but this is a potentially relevant narrative review (exclude)

188 Q4. If this is primary research, does the full text describe a study on the detection in

189 matrix, epidemiology of the exposure source, epidemiology of human exposure,

190 and/or intervention/control of the exposure source in *Cyclospora cayetanensis*?

191 a. Yes (proceed to data extraction)

192 b. No (This is a study of cyclosporiasis treatment in humans) (exclude)

- 193 c. No (This is a study of the pathogenesis of cyclosporiasis) (exclude)
- 194 d. No (This is an animal study) (specify species tested) (exclude)
- 195 e. No (This is a study of diagnosis of illness in humans) (exclude)
- 196 f. No (The study is not relevant for other reasons) (exclude)
- 197 g. This is a computer model study, a burden of illness study or a QRA (include)

198

199 The total number of articles originating from each database searched, the number remaining after
200 de-duplication, and the number of studies assessed at title/abstract and full-text screening (with
201 reasons for exclusion for the latter) will be reported in a PRISMA Flow Diagram.

202

203 *2.6. Data charting process*

204 Data charting will take place in DistillerSR®. Data will be charted from all eligible studies by
205 two reviewers working independently, using a data-charting form designed for this review that
206 was pre-tested by all reviewers on five studies, with subsequent revision for clarity and ease of
207 use before charting begins. Conflicts will be resolved through discussion or, when this is not
208 possible, by consulting a third reviewer. Authors of eligible studies will not be contacted for
209 clarification/additional information.

210

211 *2.7. Data items*

212 Reviewers will extract the following categories of data:

213

214 **Study types:**

215 Primary research

216 Quantitative risk assessment

217 *In silico* model

218 Burden of illness study

219 Systematic review*

220 Scoping review*

221 * As our preliminary search did not detect any systematic or scoping reviews, we expect that we
222 may not find either of these types of studies in the final database search.

223

224 The following data will be collected for primary research studies only:

225 **General study characteristics:**

226 Year(s) and month(s) of study conduct if reported

227 Location (country) in which the study was conducted

228

229 **What was the purpose of the study?**

230 1. Epidemiology (incl. transmission to humans, to the environment, to food)

231 1.1. Human infection

232 1.1.1. What was the study population?

233 1.1.1.1. Outbreak

234 1.1.1.2. Non-outbreak

235 1.1.1.2.1 If non-outbreak, specify the population

- 236
- Immuno-compromised, organ transplant, HIV, etc.
- 237
- Hospital cases (immune state not specified) – retrospective
- 238 evaluation of cases

- 262 2. Detection Method Development and Validation Study
- 263 2.1. Specify matrix (water, soil, human feces, etc.)
- 264 2.2. What stage of the life cycle of *Cyclospora* are they detecting?
- 265 2.3. Natural or challenge
- 266 2.4. What detection methods were used (PCR, Light microscopy, UV microscopy, Other)?

267 3. Control (intervention) study

- 268 3.1. What was the matrix (exposure source or Petri dish) they applied the intervention to?
- 269 3.1.1. If it's a matrix, at what stage was the intervention applied (pre-harvest, post-
- 270 harvest, etc.)?
- 271 3.1.2. What life cycle stage of *Cyclospora* was the control used against?
- 272 3.1.3. Natural infection vs challenge
- 273 3.1.4. What was the control (intervention) used? (type, method of application)
- 274 3.1.5. Describe the comparison group.

275

276 *2.8. Critical appraisal of individual sources of evidence*

277 As this is a scoping review, we will not conduct a critical appraisal of the literature.

278

279 *2.9. Synthesis of results*

280 The results will be summarized with descriptive statistics reporting the frequency of topics

281 investigated using a combination of tables and narrative text. Results of this review will be used

282 to identify knowledge gaps and help prioritize research directions, including areas for potential

283 systematic review for the control of *Cyclospora cayetanensis* in produce.

284

285 **Funding**

286 This study was funded by the United States Food and Drug Administration.

287

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