Epidemiology, detection, and intervention/control of

*Cyclospora cayetanensis*: A scoping review protocol

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Abstract

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

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

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

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

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

1.1. Rationale

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

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

*C. cayetanensis* was first reported in humans in 1979 (Ashford, 1979) but it was not fully identified until the early 1990s (Ortega and Sanchez, 2010). The literature base on this organism consequently appears to be relatively limited; preliminary searches for existing scoping reviews and systematic reviews of *Cyclospora* were conducted on December 12th, 2019 in MEDLINE® (Web of Science™) (dates searched: 1950-Present), Agricola (ProQuest) (dates searched: 1970-
Present), and CABI Global Health (dates searched: 1973-present) using the search terms "Cyclospora" AND "systematic review" and "Cyclospora" AND "scoping review". The same search was conducted in Food Science and Technology Abstracts (EBSCOhost) on January 3rd 2020. No scoping or systematic reviews of Cyclospora were found.

1.2. Objectives

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

2. Methods

2.1. Protocol and registration

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

2.2. Eligibility criteria

Studies included in the review must be:

1) published in English (though studies in English from any part of the world are eligible);
2) primary research, systematic reviews, scoping reviews, or quantitative risk assessments (QRA) only. Narrative or non-systematic reviews will not be eligible for inclusion, as the absence of reported methods precludes the assessment of rigor and comprehensiveness;

3) studies of Cyclospora cayetanensis, as this is the only species of Cyclospora that causes cyclosporiasis in humans (CDC, 2019). Studies that report only Cyclospora species but do not specify that the organism is C. cayetanensis will therefore not be eligible; 4) studies of any life stage (oocysts, sporocysts, or sporozoites) in any exposure source (soil, water and plants-based food).

In humans, direct person-to-person transmission of cyclosporiasis does not occur (CDC, 2019) therefore this is not of interest to the review. According to the CDC, animals have not been documented as an intermediate or primary host of C. cayetanensis and therefore animal studies are not of interest. Studies of the diagnosis of human illness, pathogenesis, and treatment of cyclosporiasis are not eligible for this review.

2.3. Information sources

To identify relevant studies, the following databases will be searched from 1979 to the present: MEDLINE® (Web of Science™), Agricola (ProQuest), CABI Global Health, and Food Science and Technology Abstracts (EBSCOhost). As the focus of this scoping review is broad and the topic is relatively new, we consider it appropriate to conduct a simple search (with no restrictions on study design or research focus) that will not require specialized information retrieval knowledge; therefore the review team designed the search without input from a library scientist. Results of the database searches will be uploaded into Endnote® X8 Desktop for de-duplication. The resulting de-duplicated results will be imported into DistillerSR® (Evidence
Partners, Ottawa, ON, Canada) review management software for further de-duplication. We will also scan the reference lists of ten (subject to availability) of the most recently published narrative reviews for additional relevant studies. We will not be contacting authors to identify additional studies.

2.4. Search

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

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

<table>
<thead>
<tr>
<th>Search no.</th>
<th>Search string</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>TS=cyclospora Indexes=MEDLINE Timespan=1979-2020</td>
</tr>
</tbody>
</table>
There will be no document type or language restrictions.

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

<table>
<thead>
<tr>
<th>Search no.</th>
<th>Search string</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>cyclospora OR cyclosporiasis OR cayetanensis</td>
</tr>
</tbody>
</table>

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

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

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

<table>
<thead>
<tr>
<th>Search no.</th>
<th>Search string</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(cyclospora) OR (cyclosporiasis) OR (cayetanensis) AND yr:[1979 TO 2020]</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>Search no.</th>
<th>Search string</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(cyclospora) OR (cyclosporiasis) OR (cayetanensis) AND yr:[1979 TO 2020]</td>
</tr>
</tbody>
</table>

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

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

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

a. Yes (proceed to full-text screening)

b. No (exclude)

c. Unclear (proceed to full-text screening)

d. No, but it may be a relevant narrative review (exclude)
The full-text screening form was pre-tested by all reviewers on five records and revised for clarity and consistency prior to the beginning of screening. This form comprises the following questions:

Q1. Is the full text available in English?
   a. Yes (proceed to Q2)
   b. No, the full text is not in English (exclude) Specify language __________
   c. No, the full text is not available (exclude)

Q2. Does the full text describe a study on *Cyclospora cayetanensis*?
   a. Yes (proceed to Q3)
   b. No (The study is of a different species of *Cyclospora*) (exclude)
   c. No (The study is not on *Cyclospora* at all) (exclude)

Q3. Does the full text describe primary research, a systematic review, a scoping review, a computer model study, a burden of illness study or a QRA of *Cyclospora cayetanensis*?
   a. Yes (proceed to Q4)
   b. No (exclude)
   c. No but this is a potentially relevant narrative review (exclude)

Q4. If this is primary research, does the full text describe a study on the detection in matrix, epidemiology of the exposure source, epidemiology of human exposure, and/or intervention/control of the exposure source in *Cyclospora cayetanensis*?
   a. Yes (proceed to data extraction)
   b. No (This is a study of cyclosporiasis treatment in humans) (exclude)
c. No (This is a study of the pathogenesis of cyclosporiasis) (exclude)

d. No (This is an animal study) (specify species tested) (exclude)

e. No (This is a study of diagnosis of illness in humans) (exclude)

f. No (The study is not relevant for other reasons (exclude)

g. This is a computer model study, a burden of illness study or a QRA (include)

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

2.6. Data charting process

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

2.7. Data items

Reviewers will extract the following categories of data:

Study types:

Primary research
Quantitative risk assessment

In silico model

Burden of illness study

Systematic review*

Scoping review*

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

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

**General study characteristics:**

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

Location (country) in which the study was conducted

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

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

1.1. Human infection

1.1.1. What was the study population?

1.1.1.1. Outbreak

1.1.1.2. Non-outbreak

1.1.1.2.1 If non-outbreak, specify the population

- Immuno-compromised, organ transplant, HIV, etc.

- Hospital cases (immune state not specified) – retrospective evaluation of cases
• Non-hospitalized Non-immunocompromised populations
  (health workers, agricultural workers, etc.)

1.1.1. Prevalence study
1.1.1.1. Prevalence of the organism or some molecular subtype of the organism
1.1.1.2. Demographics of the exposed population

1.1.2. Risk Factor study
1.1.2.1. What risk factors were investigated (could include genotype)?

1.2. Exposure source
1.2.1. Specify exposure source(s) evaluated (berries/food, water, soil)
1.2.1.1. If produce, specify the type of produce investigated.
1.2.1.1.1. If produce, specify: fresh vs frozen, domestic vs imported, processed vs unprocessed, hand-picked vs mechanically harvested
1.2.1.2. If water, specify recreational, irrigation, natural, runoff, sewage
1.2.1.3. If soil, specify agricultural, compost, other

1.2.2. Specify if this was an Outbreak or a Non-outbreak study.

1.2.3. What was the purpose of the study? (Prevalence or Risk Factor study)
1.2.3.1. If this was a Prevalence study, did the authors report the prevalence of the organism and/or molecular subtypes of the organism?
1.2.3.2. If this was a Risk Factor study, what factors were investigated?

1.3. Molecular Characterization of Cyclospora
2. Detection Method Development and Validation Study

2.1. Specify matrix (water, soil, human feces, etc.)

2.2. What stage of the life cycle of Cyclospora are they detecting?

2.3. Natural or challenge

2.4. What detection methods were used (PCR, Light microscopy, UV microscopy, Other)?

3. Control (intervention) study

3.1. What was the matrix (exposure source or Petri dish) they applied the intervention to?

3.1.1. If it's a matrix, at what stage was the intervention applied (pre-harvest, post-harvest, etc.)?

3.1.2. What life cycle stage of Cyclospora was the control used against?

3.1.3. Natural infection vs challenge

3.1.4. What was the control (intervention) used? (type, method of application)

3.1.5. Describe the comparison group.

2.8. Critical appraisal of individual sources of evidence

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

2.9. Synthesis of results

The results will be summarized with descriptive statistics reporting the frequency of topics investigated using a combination of tables and narrative text. Results of this review will be used to identify knowledge gaps and help prioritize research directions, including areas for potential systematic review for the control of Cyclospora cayetanensis in produce.
Funding

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References


