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Intestinal protozoa in travelers

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Conflict of interest: none

Topics

1. Introduction
2. Intestinal protozoa: update
   - Diagnostics
   - Epidemiology
   - Outlook: new pathogens?

Journal of Travel Medicine ISTM

Original Article

Intestinal protozoa in returning travellers: a GeoSentinel analysis from 2007 to 2019

Thomas Weitzel, MD[1,2], Ashley Brown, MPH[3], Michael Libman, MD[4], Cecilia Perret, MD[5], Ralph Huits, MD[6], Lin Chen, MD[7], Daniel T. Leung, MD[8], Karin Leder, MD[9], Bradley A. Connor, MD[10], Marta D. Menéndez, MD[11], Hilmir Asgeirsson, PhD[12,13], Eli Schwartz, MD[14,15], Fernando Salvador, MD[16,17], Denis Malvy, MD[18], Mauro Saio, MD[19], Francesca F. Norman, MD[20,21], Bhawana Amatya, MD[22], Alexandre Duvignaud, MD[18], Stephen Vaughan, MD[23], Marielle Glynn, MSc[3], On behalf of the GeoSentinel Network† and Kristina M. Angelo, DO[3]

J Travel Med May 2024

https://doi.org/10.1093/jtm/taae010

Introduction

Post-travel surveillance: GeoSentinel

(Cases per 1000 ill travelers)

Diagnosis	All Regions (N=17,353)
Systemic febrile illness‡	226
Acute diarrhea‡	222
Dermatologic disorder‡	170
Chronic diarrhea‡	113
Nondiarrheal gastrointestinal disorder‡	82
Respiratory disorder‡	77
Nonspecific symptoms or signs‡	70

Clinical manifestations

- 42% gastrointestinal
- 23% fever
- 17% cutaneous

During travel: prospective cohort (Berlin)

43% of 658 travelers reporting health problems

Table 3 Reported Illness during Travel*

Symptoms	n (%†)
Gastrointestinal	228 (80.9/34.6)
Respiratory	90 (31.9/13.7)
Fever	41 (14.5/6.2)
Dermatologic	27 (9.6/4.1)

*n = 658.

†Percent of travelers who reported illness/percent of all travelers.

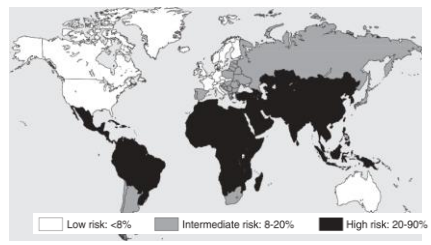
Clinical manifestations

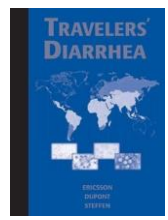
- 35% gastrointestinal
- 14% respiratory
- 6% fever
- 4% cutaneous

Freedman D et al. *New Engl J Med* **2006**
Rack J et al. *J Travel Med* **2005**

Travelers diarrhea and intestinal parasites

- Travelers diarrhea
  - Frequent, mostly infectious, mostly bacterial
- Acute TD
  - Rarely caused by protozoa (0-12%)
- Longer lasting TD
  - Persistent (<2 weeks): 3%-10%
  - Chronic (>4 weeks): 1%-3%
  - Mostly caused by protozoa
  - Might indicate onset of noninfectious gastrointestinal disease
  - Future studies needed





1st Edition 2003

TD and intestinal parasites

Spectrum

- *Giardia intestinalis*
- *Entamoeba histolytica*
- *Cryptosporidium* spp.
- *Cyclospora cayetanensis*
- *Cystoisospora belli*
- Microsporidia
- Uncertain: *Dientamoeba fragilis*
- Rarely: helminths
  - *Strongyloides stercoralis*
  - *Trichinella spiralis*
  - *Capillaria philippinensis*

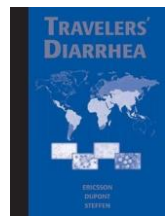
JOURNAL ARTICLE

Persistent abdominal symptoms: a persistently neglected topic in travel medicine Get access

Eli Schwartz, MD ✉, Bradley A Connor, MD

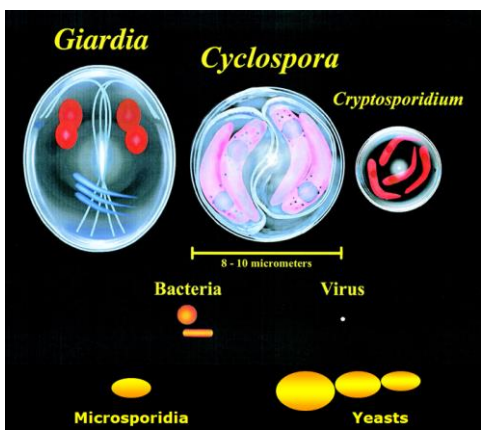
Journal of Travel Medicine, Volume 29, Issue 4, May 2022, taac016, https://doi.org/10.1093/jtm/taac016

Published: 16 March 2022 **Article history**



1st Edition 2003

Diagnosis of intestinal protozoa

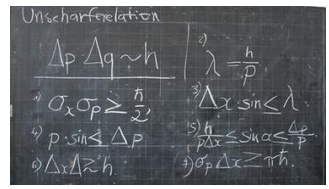


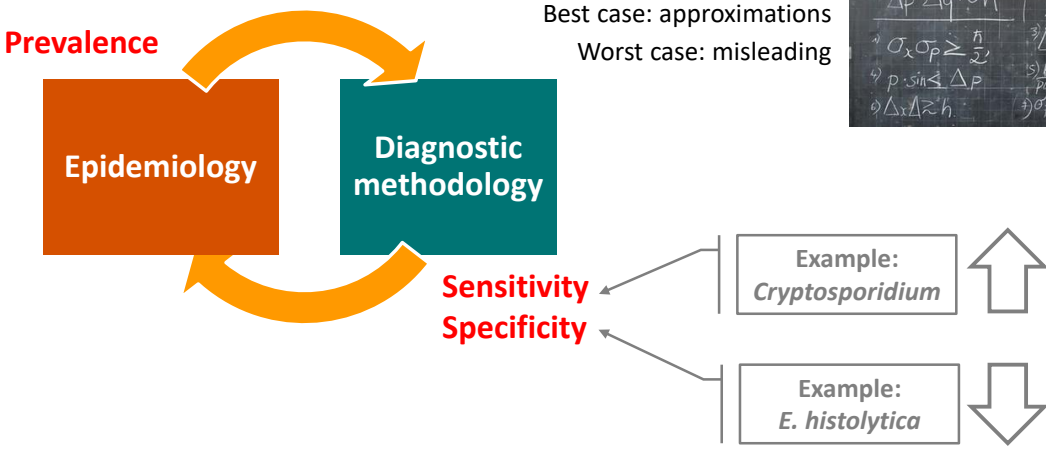
Detection method	Routine lab	Specialized lab
Microscopy (fresh stool)	+	+
Microscopy (concentration)	+	+
Antigen detection (ELISA)	+	+
Special stains		+
Direct immunofluorescence		+
Antibody detection		+(Eh)
Molecular: pathogen-specific		(+)
Molecular: multiplex	+	+

→ Most settings: only *Giardia* reliably detectable by rountine methods

Epidemiology of intestinal protozoa

Relevant uncertainties
Best case: approximations
Worst case: misleading





Intestinal protozoa in travelers: surveillance data

GeoSentinel 1996-2004: ill travelers (n = 17,353)
- *Giardia duodenalis* n = 173
- *E. histolytica* n = 120

GeoSentinel 1997-2011: ill travelers USA (n = 141,789)
- *Giardia duodenalis* n = 376
- *Blastocystis* spp. n = 289

EuroTravNet 2008: ill travelers Europe (n = 6957)
- *Giardia duodenalis* n = 193
- "Amebas" n=25
- *Cryptosporidium* spp. n=16
- *Cyclospora cayetanensis* n = 12

GeoSentinel 2007-2011: ill travelers (n = 42,173)
- *Giardia duodenalis* n = 1426
- *E. histolytica* n = 340
- *Dientamoeba fragilis* mentioned
- *Cryptosporidium* spp. mentioned

1996

2014

GeoSentinel 1996-2005: gastrointestinal infections (n=7442)
- *Giardia duodenalis* n = 810 (27.9%)
- *E. histolytica* *n* = 363 (12.5%)
- *Dientamoeba fragilis* n= 116 (4.0%)
- *Cryptosporidium spp.* n = 32 (1.1%)
- *Cyclospora cayetanensis* n = 31 (1.1%)
- *Cystoisospora belli* n = 3 (0.1%)

Munich 1999-2014: ill travelers (n = 16,817)
- *Blastocystis* spp. n = 900
- *Giardia duodenalis* n = 730
- *Entamoeba* spp. n = 130
- *Cryptosporidium* spp. n = 53
- *Cyclospora cayetanensis* n = 37

Freedman D et al. *New Engl J Med* **2006**
Harvey K et al. *MMWR* **2013**
Field V et al. *BMC Infect Dis* **2010**
Leder K et al. *Ann Int Med* **2013**
Swaminathan A et al. *J Infect* **2009**
Herbinger KH et al. *Am J Trop Med Hyg* **2016**

Experience from Berlin 2006

- Post-travel prolonged/chronic intestinal problems: frequent and clinically diverse
  - Diarrhea
  - Pain/malaise
  - Bloating …
- It pathogen found
  - 70-80% parasitic

Institute of Tropical Medicine and International Health Berlin (2006)

Detected parasite	n	% of total	% of pathogens
1. Giardia duodenalis	187	31.6	81
2. Cryptosporidium spp.	25	4.2	10.8
3. Strongyloides stercoralis	13	2.2	5.6
4. Cyclospora cayetanensis	5	0.8	2.2
5. Cystoisospora belli	1	0.2	0.4
Non pathogenic			
Blastocystis spp.	211	35.6	
Apathogenic amoebas	150	25.3	

Unpublished data

GeoSentinel: intestinal protozoa study

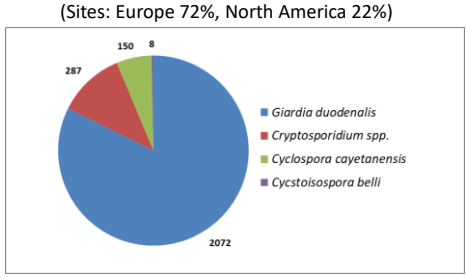
Methods

- Descriptive retrospective analysis GeoSentinel database 2007-19
- Inclusion: pathogenic intestinal protozoa (except *Entamoeba histolytica*)

Results

- Total patients: n = 2507 (2517 infections)

(Sites: Europe 72%, North America 22%)

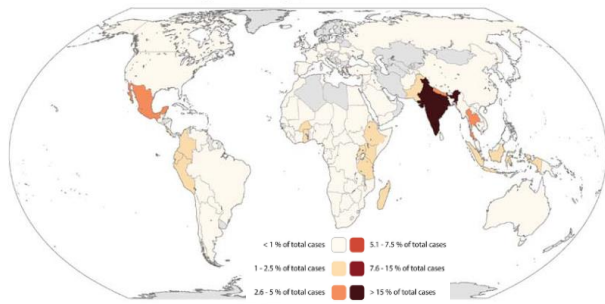


	Giardiasis N= 2072	Cryptosporidiosis N = 287	Cyclosporiasis N = 150
Female	53.2%	58.2%	50.7%
Age, median (years)	31	28	43
<18 years	5%	13.9%	2.0%
18-39 years	62.2%	51.3%	38.7%
40-59 years	24.5%	16.4%	42.7%
≥60 years	8.3%	8.4%	1.3%
Tourism	64.9%	65.5%	70%
Aid work/mission.	14.0%	10.5%	8.7%
Business	10.4%	5.2%	13.3%
VFR	7.1%	15.7%	6.0%
Trip duration, median (d)	30	18	19
Onset to visit, median (d)	30	11	19
Hospitalized	4.3	14.2	6.4
Pretravel consultation	66.5	48.3	51.5

Giardiasis: exposure data

	Giardiasis (n = 2,072)	Cryptosporidiosis (n = 287)	Cyclosporiasis (n = 150)
South Central Asia	45,8	19,5	12,7
Sub-Saharan Africa	22,6	24,7	2,7
South America	8,7	6,3	8
South East Asia	7,7	13,6	31,3
Central America	5,3	12,2	27,3
Middle East	2,2	3,1	1,3
North Africa	2,2	3,8	0
Caribbean	2	7,3	10
Western Europe	1,5	5,2	0
North East Asia	0,8	0,7	4
Eastern Europe	0,5	1,4	0
North America	0,4	1,1	0,7
Oceania	0,2	1,1	1,3
Australia/New Zealand	0,1	0	0,7

Percentage of total giardiasis cases (N = 2,072)



Top-5 of 132 countries

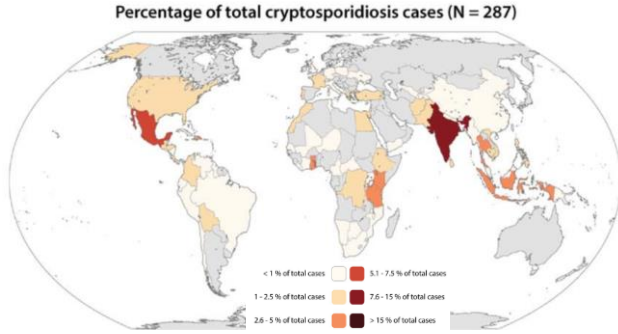
1. India n=810 (39.1%)
2. Nepal n=75 (3.6%)
3. Thailand n=60 (2.9%)
4. Mexico n=52 (2.5%)
5. Peru n=50 (2.4%)

Weitzel et al. *J Travel Med* **2024**

Cryptosporidiosis: exposure data

	Giardiasis (n = 2,072)	Cryptosporidiosis (n = 287)	Cyclosporiasis (n = 150)
South Central Asia	45,8	19,5	12,7
Sub-Saharan Africa	22,6	24,7	2,7
South America	8,7	6,3	8
South East Asia	7,7	13,6	31,3
Central America	5,3	12,2	27,3
Middle East	2,2	3,1	1,3
North Africa	2,2	3,8	0
Caribbean	2	7,3	10
Western Europe	1,5	5,2	0
North East Asia	0,8	0,7	4
Eastern Europe	0,5	1,4	0
North America	0,4	1,1	0,7
Oceania	0,2	1,1	1,3
Australia/New Zealand	0,1	0	0,7

Percentage of total cryptosporidiosis cases (N = 287)



Top-5 of 83 countries

1. India n=35 (12.2%)
2. Mexico n=21 (7.3%)
3. Tanzania n=14 (4.9%)
4. Thailand n=12 (4.2)
5. Ghana n=9 (3.1%)
   Indonesia n=9 (3.1%)

Weitzel et al. *J Travel Med* **2024**

Experience from Berlin

CMI CLINICAL MICROBIOLOGY AND INFECTION

Epidemiological and clinical features of travel-associated cryptosporidiosis

T. Weitzel[1], O. Wichmann[1], N. Mühlberger[1], B. Reuter[2], H-D. Hoof[3] and T. Jelinek[1]

Methods

- Time span: 2000-2004
- Detection: direct immunoflourescence (Merifor)

Results

- **57 travelers** with *Cryptosporidium* spp.
- 2.8% of diarrhea post-travel

Associated factors

- Exposure: Asia (India) > Latin America > Africa
- Duration: longer trips
- Style: backpacking

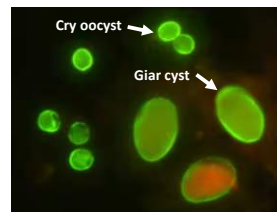


Photo: DPDx

Clinical presentation

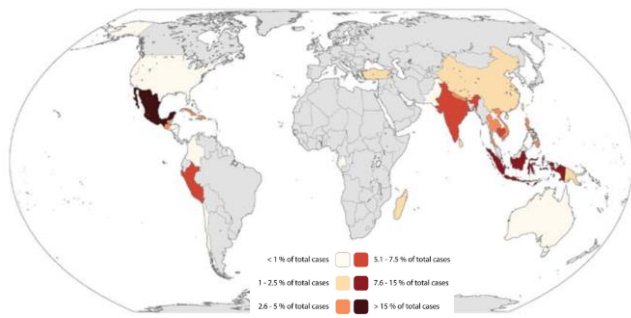
Diarrhea	91%
Abdominal pain	69%
Fatigue	56%
Bloating	40%
Anorexia	31%
Fever	30%
Nausea	27%
Weight loss	24%
Arthralgia	15%,
Vomiting	13%
Headache	13%

Weitzel et al. *Clin Microbiol Infet* **2006**

Cyclosporiasis: exposure data

	Giardiasis (n = 2,072)	Cryptosporidiosis (n = 287)	Cyclosporiasis (n = 150)
South Central Asia	45,8	19,5	12,7
Sub-Saharan Africa	22,6	24,7	2,7
South America	8,7	6,3	8
South East Asia	7,7	13,6	31,3
Central America	5,3	12,2	27,3
Middle East	2,2	3,1	1,3
North Africa	2,2	3,8	0
Caribbean	2	7,3	10
Western Europe	1,5	5,2	0
North East Asia	0,8	0,7	4
Eastern Europe	0,5	1,4	0
North America	0,4	1,1	0,7
Oceania	0,2	1,1	1,3
Australia/New Zealand	0,1	0	0,7

Percentage of total cyclosporiasis cases (N = 150)



Top-5 of 32 countries

1. Mexico n=32 (21.3%)
2. Indonesia n=22 (14.7%)
3. Peru n=9 (6.0%)
4. India n=8 (5.3)
   Cambodia n=8 (5.3%)

Weitzel et al. *J Travel Med* **2024**

Santiago 2016-23: *Cyclospora* cases

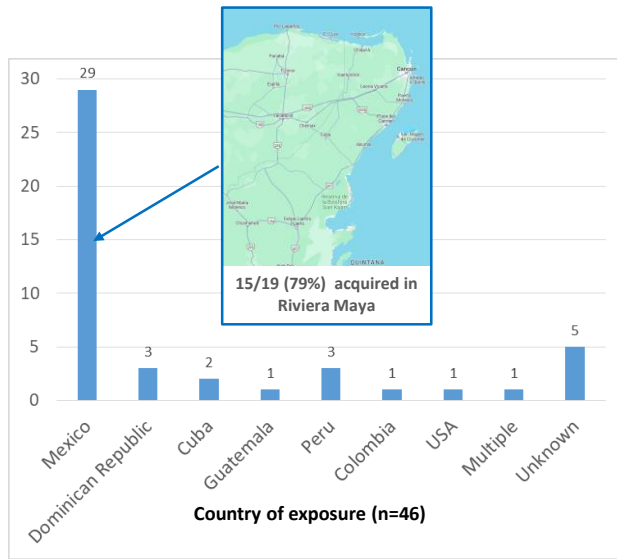
Ongoing monocentric study
(Clinica Alemana, Santiago, Chile)

Methods

- Descriptive retrospective analysis
- Lab data: *Cyclospora cayetanensis* detected in rountine samples (FilmArray + Kinyoun)
- Metadata: clinical files and interview

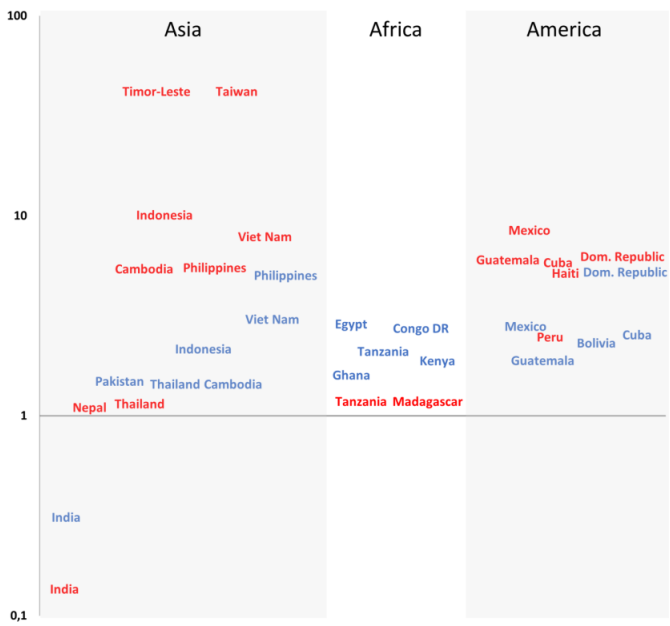
Results

- Detected cases: n = 46



Weitzel T. Unpublished data

Relative frequence compared to giardiasis



Country-specific relative proportions compared to giardiasis (logarithmic scale)

Blue = cryptosporidiosis
Red = cyclosporiasis

Weitzel et al. *J Travel Med* **2024**

Conclusions: epidemiology

Giardia lamblia

- "Typical traveler": young adult tourist, 4-week trip
- Exposure: India
- Presenting 4 weeks after illness onset
- Rarely severe (4% hospitalized)

Compared to giardiasis:

Cryptosporidium spp.

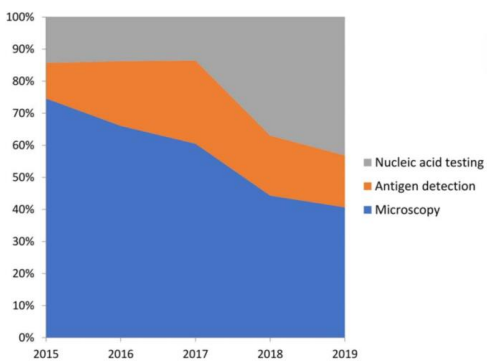
- Shorter trip duration
- Exposure: more diverse
- More the younger patients
- More in VFR, less in business travelers
- Presenting 1-2 weeks after illness onset
- More severe (14% hospitalized)

Compared to giardiasis:

Cyclospora cayetanensis

- Shorter trip duration
- Exposure: more diverse with certain hotspots (Mexico, Indonesia)
- More the older patients
- More in business travelers, more in aid workers
- Presenting 1-2 weeks after illness onset
- More severe? (6% hospitalized)

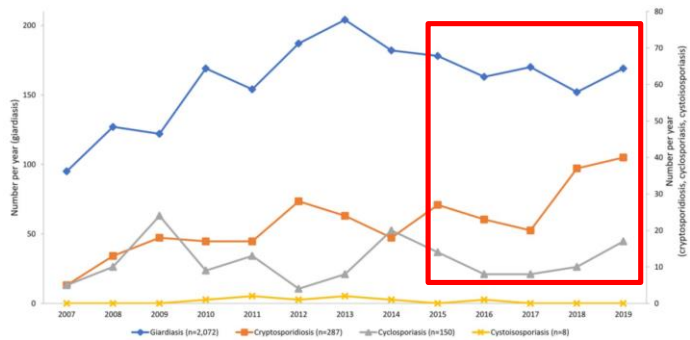
GeoSentinel 2015-19: diagnosic methods and case numbers



Applied diagnostic methods in reported protozoal infections (n = 1,224)

Annual case numbers of

- Giardiasis
- Cryptosporidiosis
- Cyclosporiasis



Weitzel et al. *J Travel Med* **2024**

Experience Santiago 2016-19

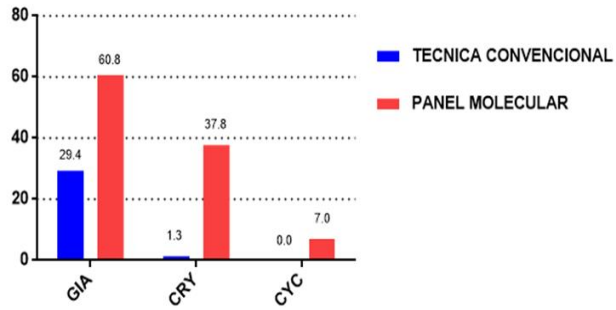
Methods

- Descriptive retrospective analysis
- Routine samples, Santiago, Chile
- Protozoa detected by gastrointestinal multiplex panel (FilmArray)

Results

- Samples: n = 10,782
- Protozoa: n = 428 (4%)
  - *Giardia duodenalis* n = 243 (2.3%)
  - *Cryptosporidium* spp. n = 150 (1.4%)
  - *Cyclospora cayetanensis* n = 28 (0.3%)
  - *Entamoeba histolytica* n = 6 (0.06%)

Average annual detection rate 2016-19



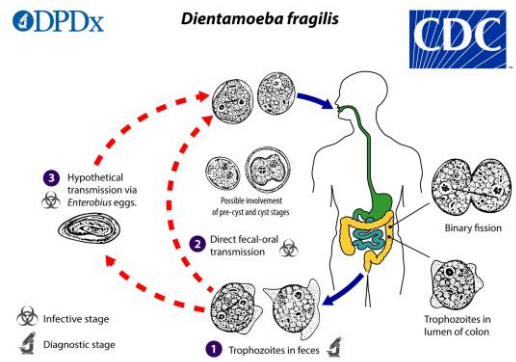
GIA, *G. lamblia*
CRY, *Cryptosporidium* spp.
CYC, *Cyclospora cayetanensis*

Pérez C, et al. *XXXVII Congreso Chileno de Infectología* **2021**

Emerging methods, emerging pathogens?

Allplex GI-Parasite Assay

- qPCR multiplex including
  - *Giardia duodenalis*
  - *Cryptosporidium spp.*
  - *Cyclospora cayetanensis*
  - *Entamoeba histolytica*
  - *Dientamoeba fragilis*
  - *Blastocystis hominis*

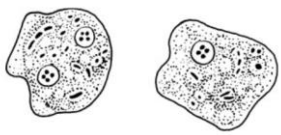


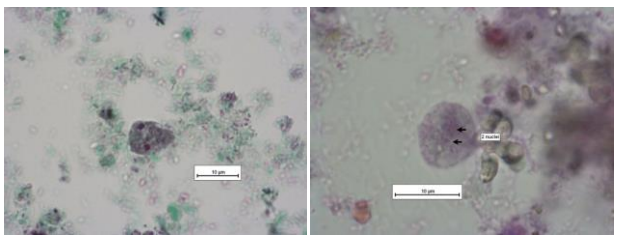
- Flagellate (without flagellum), related to *Histomonas* (bird pathogen)
- Worldwide (?)
- Transmission by *Enterobius* eggs?

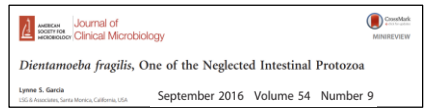
Dientamoeba fragilis

Diagnosis

- Not diagnosed with routine microcroscopy
- Requires trichrome stain (and experience)







"Dientamoeba fragilis should be included in the differential diagnosis of chronic diarrhea and eosinophilic colitis."

Clinical management (prolonged diarrhea)

- Treat if no other pathogen identified
- 1st line: paromomicin (500mg tid x7-10d)
- 2nd line: metronidazol (750mg tid x10d)

Dientamoeba fragilis in travelers

Tropical Medicine center (Israel)

Retrospective study (2017-2019)

- Prolonged diarrhea (>2 wks) post-travel
- Allplex GI-Parasite assay

Resultados

- N = 203
- *Dientamoeba fragilis*
  - Travelers: 18.7%
  - Non-travelers: 19.7%

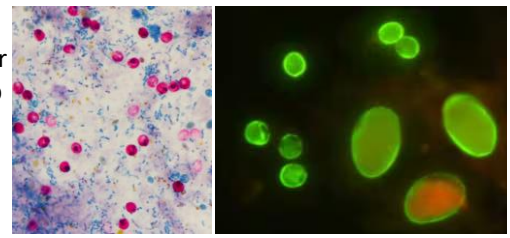
	Travellers ($n = 203$)		
Age (years): average, median (IQ)	30 (24–42)		
Sex: females	114 (56%)		
Overall positive samples	75 (36.95%)		
Protozoa	*n*	% of all samples	% of positive samples
Total per parasite*			
Blastocystis hominis	54	26.6#	72.0#
Dientamoaeba fragilis	38	18.7	50.0#
Giardia lamblia	6	3.0	8.0
Cyclospora cayetanensis	0	0	0
Cryptosporidium spp	1	0.5	1.3
Entamoeba histolytica	0	0	0
Multiple infections	20	9.9	28
Blastocystis hominis + *Dientamoaeba fragilis*	18	9.4	25.3
Blastocystis hominis + *G. lamblia*	1	0.5	1.3
G. lamblia + *Dientamoaeba fragilis*	0	0	0
Blastocystis hominis + *Dientamoaeba fragilis* + *G. lamblia*	1	0.5	1.3

Gefen-Halevi S, et al. *J Travel Med* **2022**

Take-home: diagnostics

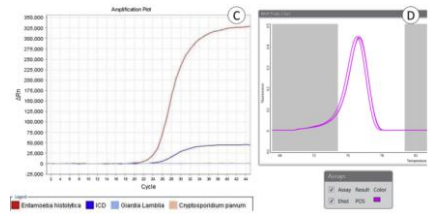
Conventional diagnostics

- Microscopy: remember additional testing for coccidia and *Strongyloides*, *E. histolytica* gap
- Coproantigen ELISAs or RDTs: easy, high sample throughput, limited <u>sensitivity</u>

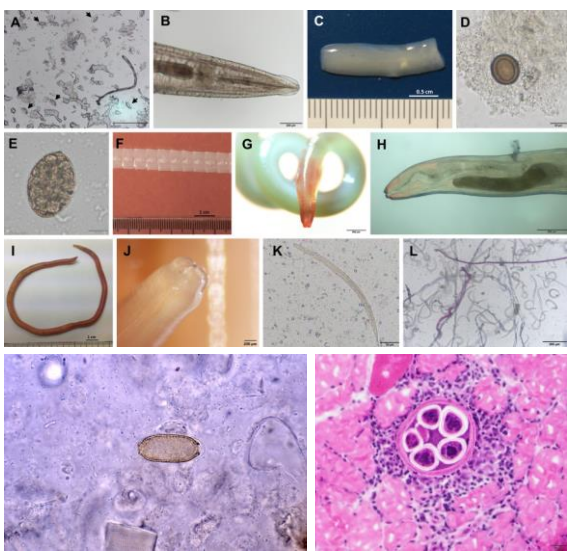


Multiplex molecular assays

- Higher sensitivity: all protozoa
- Higher specificity: *E. histolytica*
- Remember gaps (*Cystoisospora*, *Strongyloides*)
- New perspectives, e.g. *Dientamoeba fragilis*
- Drawback: few clinical evaluations, very expensive



E. histolytica in liver abscess aspirate



Best regards from all the parasites in Chile

Questions or comments:

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