

Strongiloidiasi



Federico Gobbi

Centro Malattie Tropicali



NEGRAR - VERONA - ITALY

Centre for Tropical Diseases



available at www.sciencedirect.com



journal homepage: www.elsevierhealth.com/journals/trst



REVIEW

Strongyloidiasis – the most neglected of the neglected tropical diseases?

Annette Olsen^{a,*}, Lisette van Lieshout^b, Hanspeter Marti^c, Ton Polderman^b,
Katja Polman^d, Peter Steinmann^{e,f}, Russell Stothard^g, Søren Thybo^h,
Jaco J. Verweij^b, Pascal Magnussen^a

Epidemiology



Strongyloides stercoralis: “Neglected conditions”

“Some 30–100 million people are estimated to be infected worldwide (probably an underestimate)”

http://www.who.int/neglected_diseases/diseases/strongyloidiasis/en/

Strongyloides stercoralis: A Plea for Action

Zeno Bisoffi^{1,2*}, Dora Buonfrate^{1,2}, Antonio Montresor³, Ana Requena-Méndez^{2,4}, Jose Muñoz^{2,4}, Alejandro J. Krolewiecki⁵, Eduardo Gotuzzo^{2,6}, Maria Alejandra Mena^{2,6}, Peter L. Chiodini^{2,7}, Mariella Anselmi^{2,8}, Juan Moreira^{2,8}, Marco Albonico^{1,2,9}

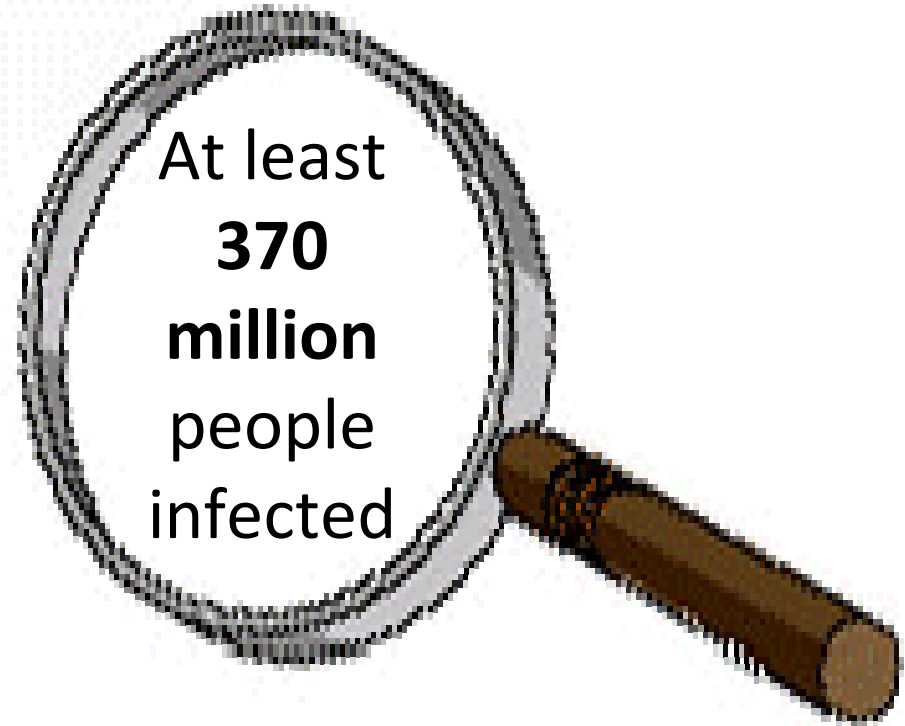


Figure 1. Embryonated eggs of *Strongyloides stercoralis* in bronchial fluid from a fatal case of disseminated strongyloidiasis (photo by Maria Gobbo, CTD Negrar, Verona).

***Strongyloides stercoralis*: a plea for action**

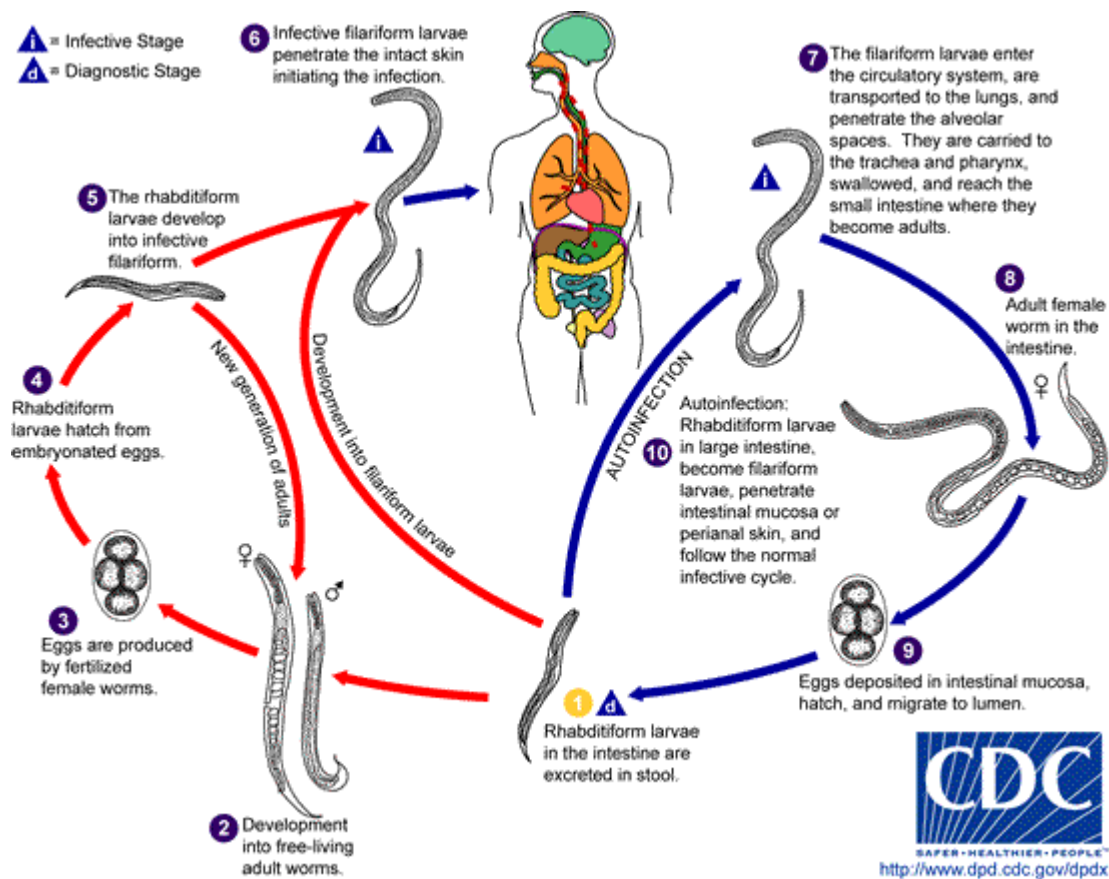


~~Some 30–100 million people are
estimated to be infected
worldwide
(probably an underestimate)”~~

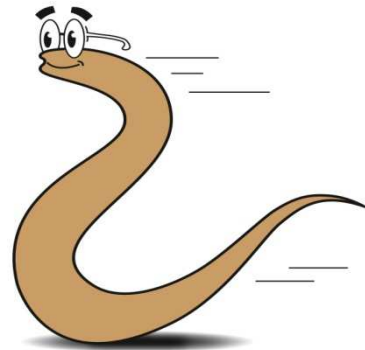


At least
370
million
people
infected

Ciclo vitale



Trasmissione



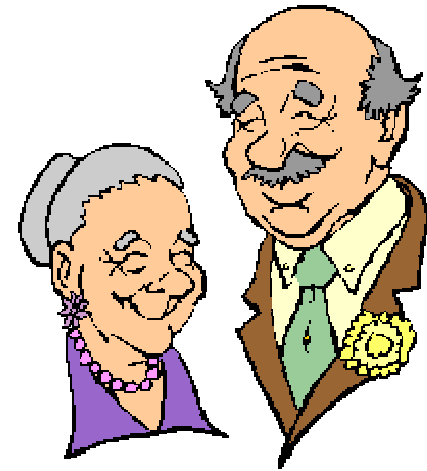
Autoinfezione



SAFER • HEALTHIER • PEOPLE™
<http://www.dpd.cdc.gov/dpdx>

Caso n. 1

- Ottantenne veronese
- Deperisce di giorno in giorno
- Dimagrimento (10 Kg)
- Non ha più forze



“Penso che mia moglie mi stia avvelenando”

Prevalence in Italy: memories of the past...



Silvana Mangano in "Riso amaro" (1949)

Reemergence of Strongyloidiasis, Northern Italy

Abrescia FF, Falda A, Caramaschi G, et al. *Emerg Infect Dis* 2009; 15(9): 1531-1533



(age ≥ 65 , eosinophil count ≥ 500 cells/ μ L)

37 (28%) of 132 patients **positive**

Prevalence of strongyloidiasis in North East Italy – preliminary data from an observational serosurvey*

Dora Buonfrate¹, Fabrizio Abrescia¹, Giacomo Caramaschi², Monica Degani¹, Mario Giobbia³, Marta Mascarello⁴, Maria Merelli⁵, Paola Rodari⁶, Novella Scattolo⁷, Stefano Tais¹, Giuseppina Napoletano⁸, Zeno Bisoffi¹.

- Arruolamento di italiani (nati prima del 1951) e stranieri (maggioirenni) a partire dai laboratori analisi
- “Casi” > 500 eos/ μ L
- “Controlli” < 500 eos/ μ L

Al momento (studio in corso), su 388 sieri 19 positivi (5%), tutti “casi” meno uno (con eos 420)

*abstract submitted to ECTMIH 2013

Altre zone del bacino del Mediterraneo...





Studio di prevalenza del 2003
sulla costa spagnola del
Mediterraneo, area di Valencia:
tasso di **prevalenza del 12,4% tra
lavoratori agricoli autoctoni**

Analisi delle caratteristiche geografiche e ambientali
dell'area: massima prevalenza in **aree pianeggianti ricche
di acque stagnanti, risaie, canali di irrigazione**



Caso n. 2

Rimini...

ha impegnato tutte le sue risorse economiche da oltre 20 anni nella vana speranza di guarire da un prurito generalizzato, persistente e incoercibile



Caso clinico 3

Lavoratore italiano all'estero

- Rientrato in vacanza dalla R. Dominicana, lamenta prurito insorto recentemente
- Eosinofilia >20%
- All'es. obiettivo si rileva...



CLINICA delle forme croniche

Quasi il 50% dei pz affetti da strongiloidiasi cronica è **asintomatico**.

Il 75% dei soggetti affetti presenta eosinofilia.



CLINICA

Sintomi cronico-ricorrenti:

- Cutanei (orticaria, prurito)
- Respiratori (tosse secca, asma ricorrente)
- Gastrointestinali (dolore addominale, pseudoappendicite, diarrea)
- Sistemici (perdita di peso, cachessia)



epigastrico,

Patogenesi

Penetrazione delle larve L3: prurito, “larva currens”, (rara),
prurito anale



Passaggio larvale nei polmoni: alterazioni transitorie tissutali e peri-vascolari: tosse secca irritativa, broncospasmo

Patogenesi

- Duodeno, digiuno: risposta infiammatoria (infiltrato linfocitario e eosinofilo, edema della lamina propria): dolore epigastrico, addominale.
- Per infestazioni più massive: enterite catarrale, con erosione dei villi: diarrea e dolori addominali ricorrenti, malassorbimento

Patogenesi

Sindrome “allergica”: prurito cutaneo diffuso, eosinofilia periferica, dermatiti papulose, eczematose, orticarioidi...

Caso clinico 4

Immigrant from Ghana, 38 years

- Diagnosis of non Hodgkin lymphoma
- Starts chemotherapy
- Sudden onset of septic fever, septic shock
- Paralytic ileus, ARDS.....
- Exitus
- The cause: disseminated strongyloidiasis, invading the whole body

Larvae in the gastric juice



Eggs and larvae in bronchial fluid

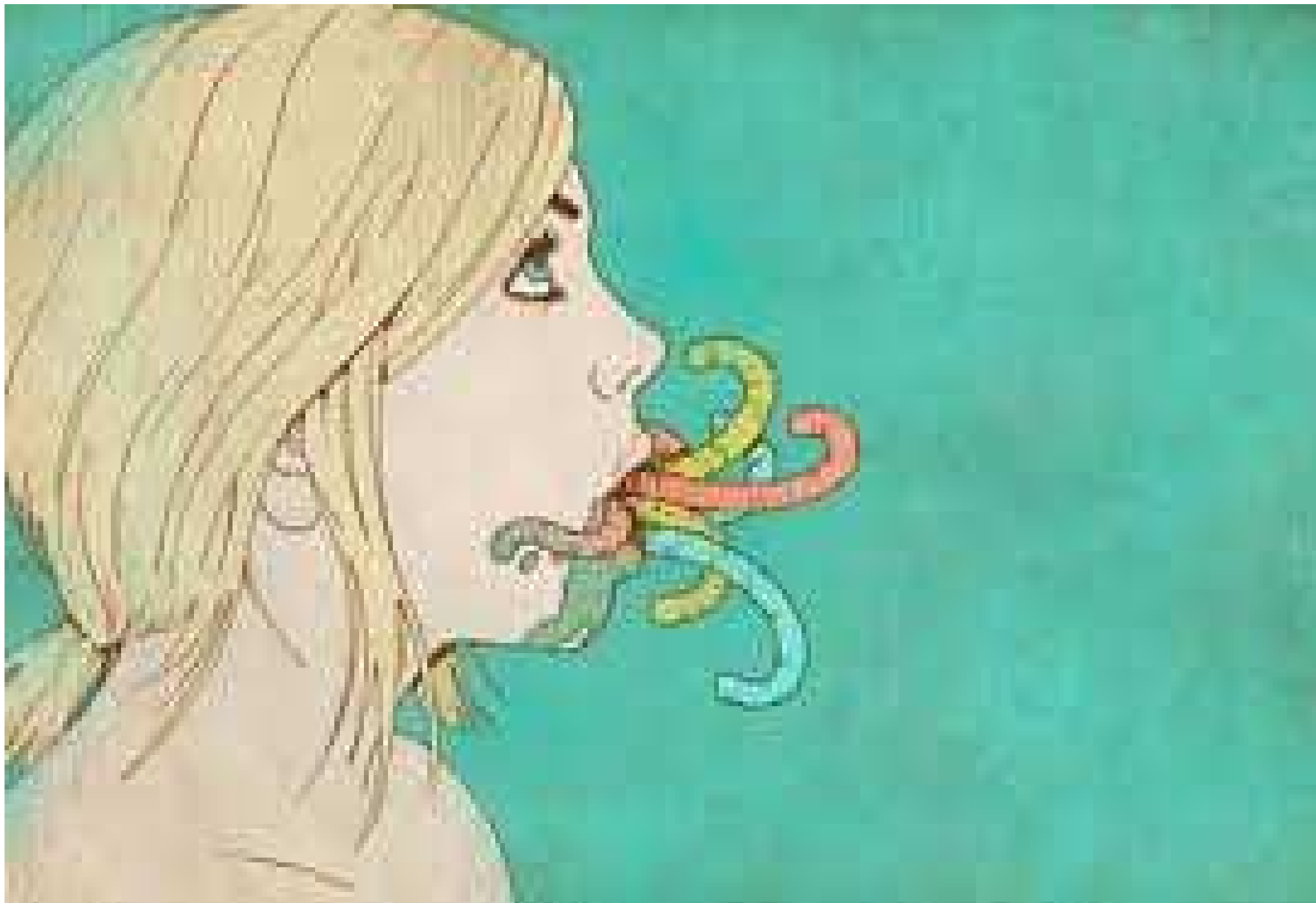






Adult female of *Strongyloides stercoralis* collected in bronchial fluid.
Scale bar = 400 μm .

Iperinfestazione e disseminazione

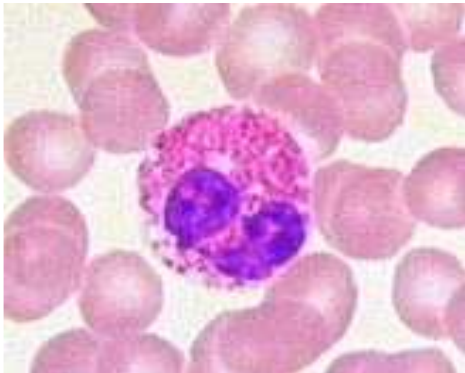


CLINICA

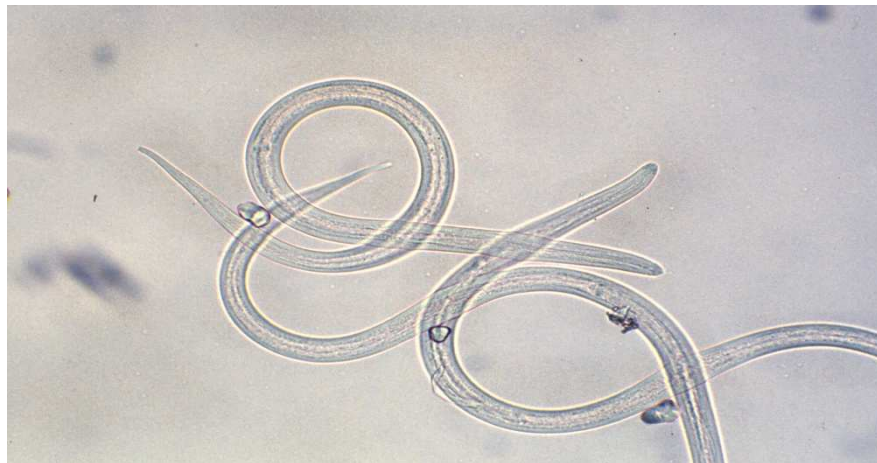
- 1. sindrome da iperinfestazione:** aumento della carica parassitaria per accelerazione dei cicli di autoinfestazione endogena in assenza di una diffusione di larve a distanza dall'usuale circuito migratorio (vie digestive ed aeree) ;
- 2. strongiloidiasi disseminata:** diffusione sistemica di larve filariformi invasive verso distretti distanti dal loro normale circuito migratorio, con potenziale invasione di ogni organo dell'organismo;

Attenzione!

Nei casi di **iperinfezione** e **strongiloidiasi disseminata**

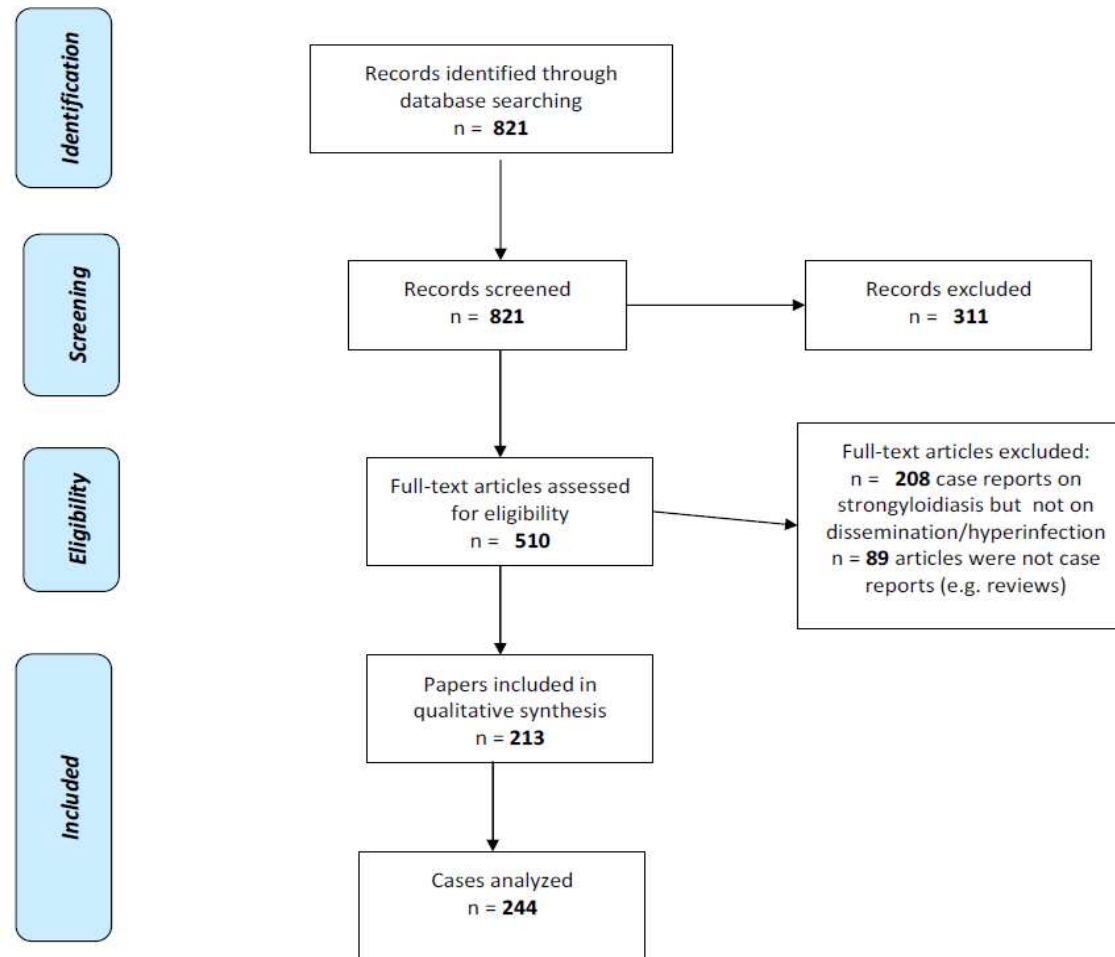


- L'eosinofilia è spesso assente
- La diagnosi viene agevolmente eseguita tramite esame microscopico diretto (numerosissime larve!)



Severe strongyloidiasis: a systematic review of case reports

Dora Buonfrate, Ana Requena-Mendez, Andrea Angheben, et al. BMC Infectious Diseases 2013, 13(1):78.



Severe strongyloidiasis: 67% patients under steroids

Table 1 Patients under steroid treatment: reasons for prescription

Condition	N (%)	References
COPD/asthma/lung fibrosis	30 (18.3)	[48,49,52,57-59,68,99,101,118,121,123,128,137,146,153,180-183,185,187,188,192-196]
Leukemia/lymphoma	13 (7.9)	[9,17,23,25,37,47,56,98,111,126,162,186]
SLE	9 (5.5)	[41,64,66,86,151,176,197,198]
Rheumatoid arthritis	4 (2.4)	[83,103,199,200]
IBD	6 (3.6)	[59,147,148,164,177,201]
Sarcoidosis	2 (1.2)	[65,132]
Cancer	8 (4.8)	[30,54,93,97,112,160,169,202]
Organ/bone marrow transplant	25 (15.2)	[21,25,29,31,39,48,51,54,60,70,71,74,76,81,87,88,90,92,94,142,145,150,184]
Glomerulonephritis/CRI	6 (3.6)	[16,18,20,129,130,154]
"Idiopathic" eosinophilia	3 (1.8)	[7]
Multiple myeloma/myelodysplasia	6 (3.6)	[72,185,203-206]
Aspecific symptoms	2 (1.2)	[85,166]
Other clinical conditions	46 (28)	[17,22,34,36,54,59,66,84,89,100,102,110,113,124,125,127,133-135,140,155,159,171-174,207-213]
HIV-related opportunistic infections/IRIS	4 (2.4)	[24,26,36,105]

Other conditions (no steroids):

HTLV 1

HIV

Alcoholism

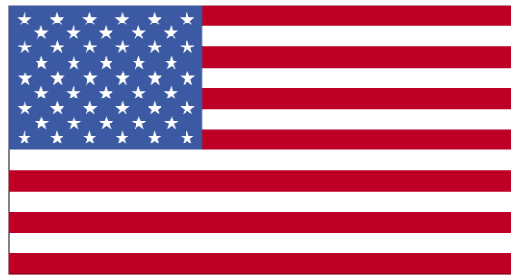
Malnutrition

Transplant

Severe strongyloidiasis: a systematic review of case reports

Dora Buonfrate, Ana Requena-Mendez, Andrea Angheben, et al. BMC Infectious Diseases 2013, 13(1):78.

One patient diagnosed with “idiopathic
hypereosinophilic syndrome”
died after BM transplant*

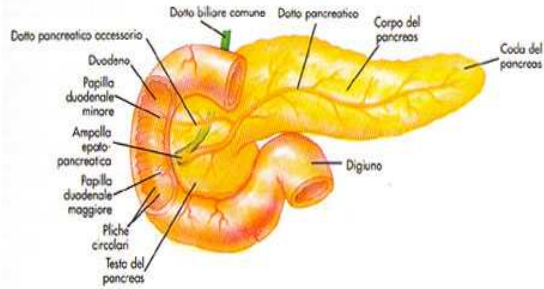
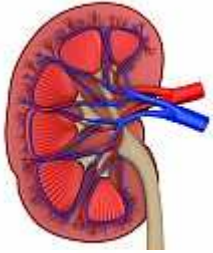


*Qazilbash et al. Bone Marrow Transplantation 2006; 38:393-394

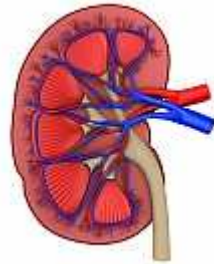


Centers for Disease Control and Prevention
CDC 24/7: Saving Lives. Protecting People.™

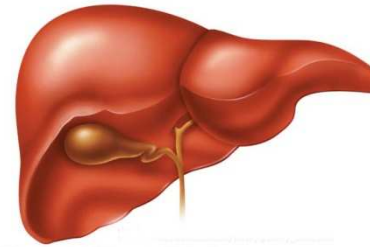
**Transmission of *Strongyloides stercoralis*
Through Transplantation of Solid Organs –
Pennsylvania, 2012
Weekly
April 12, 2013 / 62(14);264-266**



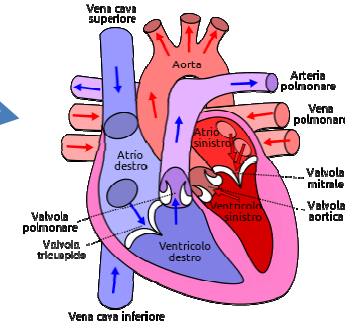
Diagnosi di strongiloidiasi, paziente trattato con successo



Diagnosi di strongiloidiasi, paziente trattato con successo



Decesso – causa indeterminata



Diagnosi di strongiloidiasi, trattato con ivermectina + albendazolo. Sepsi da G- e meningite da enterococco. **Deceduto**



Caso clinico n. 5

Coppia di sposi in viaggio di nozze 27/08-12/09/08

South East Asia (Malaysia, Singapore, Koh Samui Island)



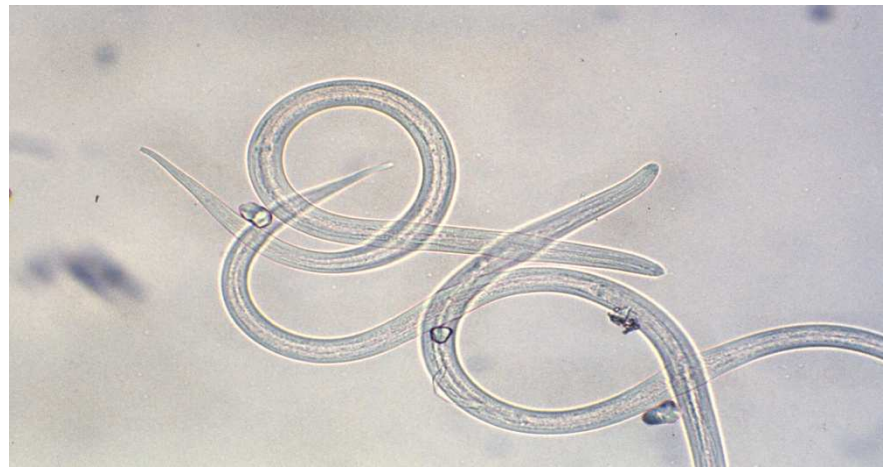
7 gg dopo il rientro lui e 10 lei comparsa di rash cutaneo orticarioide, febbre, tosse, splenomegalia.



All'arrivo presso il nostro centro (a circa 1 mese dal ritorno):

- Ipereosinofilia: 8720/mm³ lui e 8700/mm³ lei
- Rialzo di PCR : 108 e 49 mg/L con v.n. <5 mg/L
- Transaminasi mosse: ALT pari a 56 e 77 U/L

- Sierologia, esame feci per parassiti negativo per lei, positivo per lui (larve rabaditoidi di *S.stercoralis*);
- Coltura positiva per entrambi (*S.stercoralis*).



“E la fonte di acquisizione?”

Probabile fonte di infestazione

- I pazienti hanno riferito di aver camminato scalzi sull'erba intorno al bungalow a Koh Samui, non altri fattori di rischio precedenti
- Trattati: no eosinofilia, no disturbi, la sierologia si è positivizzata a un mese per entrambi (basso titolo) e poi negativizzata a sei mesi



CLINICA delle forme acute

- 1) descrizione della forma acuta in aree endemiche (comunità Aborigene dell'Australia) come sindrome diarroica con ipoproteinemia e ipokaliemia nel bambino.
- 2) descrizione di casi acuti caratterizzati da sindrome simil-Loeffler in adulti viaggiatori.

BRIEF COMMUNICATIONS

**Acute Strongyloidiasis in Italian Tourists Returning
From Southeast Asia**

Andrea Angheben, MD,* Manuela Mistretta, BSc,[†] Maria Gobbo, Medical Laboratory Technician,[†] Stefania Bonafini, Lab Assistant,[†] Tiziana Iacovazzi, MD,[‡] Alessio Sepe, MD,[§] Federico Gobbi, MD, DTM&H,* Stefania Marocco, MD, DTM&H,* Andrea Rossanese, MD, PhD,* and Zeno Bisoffi, MD, DTM&H*

*Centre for Tropical Diseases, Hospital S. Cuore – Don Calabria, Negrar, Italy; [†]Service of Epidemiology and Laboratory for Tropical Diseases, Hospital S. Cuore – Don Calabria, Negrar, Italy; [‡]Unit of Infectious Diseases, Hospital Fallacara, Triggiano, Italy; [§]Unit of Infectious Diseases, Hospital G. Rummo, Benevento, Italy

DOI: 10.1111/j.1708-8305.2010.00496.x

Strongyloidiasis is a soil-transmitted helminthiasis with worldwide distribution. Contrary to chronic form, hyperinfestation and life-threatening dissemination, first (invasive) stages of the disease are not well characterized. This paper describes two cases of acute strongyloidiasis in travelers returning from Southeast Asia and highlights the need to take strongyloidiasis into account also among acute travel-related illnesses.

CLINICA delle forme acute

Reazione cutanea pressochè immediata nel sito di entrata delle larve;

- entro 10 gg sindrome di Loeffler (ipereosinofilia, tosse, asma o irritazione tracheobronchiale, prurito o rash cutaneo orticarioide);
- dopo 2-3 settimane sintomi intestinali (diarrea, stipsi, dolore addominale, anoressia);
- larve nelle feci dopo 21-28 giorni dalla penetrazione della cute.

Acute Strongyloidiasis: A Rarity. Chronic Strongyloidiasis: A Time Bomb!

Eric Caumes MD^{1,2,*}, Jay S. Keystone MD^{3,4}

[Volume 18, Issue 2](#), pages 71–72, March/April 2011

Journal of
TRAVEL MEDICINE

- 1) We must find out people unawares carrying the time bomb
- 2) Treatment cannot but aim at completely removing the time bomb



QUINDI

La strongiloidiasi rientra in diagnosi differenziale per pazienti con febbre e/o orticaria associate ad eosinofilia al rientro da viaggio in Paesi endemici (storia di contatto cute/suolo).

NB: breve il periodo di prepatenza (entro le due settimane dall'esposizione) prima dello sviluppo del Loeffler.

Imported Strongyloidiasis: Epidemiology, Presentations, and Treatment

Dora Buonfrate • Andrea Angheben • Federico Gobbi •
Jose Muñoz • Ana Requena-Mendez •
Eduardo Gotuzzo • Maria Alejandra Mena •
Zeno Bisoffi



Methods.

We searched MEDLINE using the following search strategy:
(strongyloid* AND (Humans[Mesh] AND "last 10 years"[PDat])) AND
((travel*) OR (imported) OR (migrant*) OR (immigrant*)).

Prevalence of strongyloidiasis in migrants

Paper	Country	Population	Diagnostic method	Positive/tested subjects. N (%)
<i>Gualdieri 2011</i>	Italy	Immigrants	Microscopy	2/514 (0.4%)
<i>Hochberg 2011</i>	USA	Immigrants HIV+	Microscopy and serology	Microscopy:0/128; serology:33/128 (26%)
<i>Posey 2007</i>	USA	Refugees	Serology	214/462 Sudanese (46%); 23/100 Somali Bantu (23%)
<i>Caruana 2006</i>	Australia	Immigrants and refugees	Microscopy and serology	Microscopy:10/321 Serology:84/354

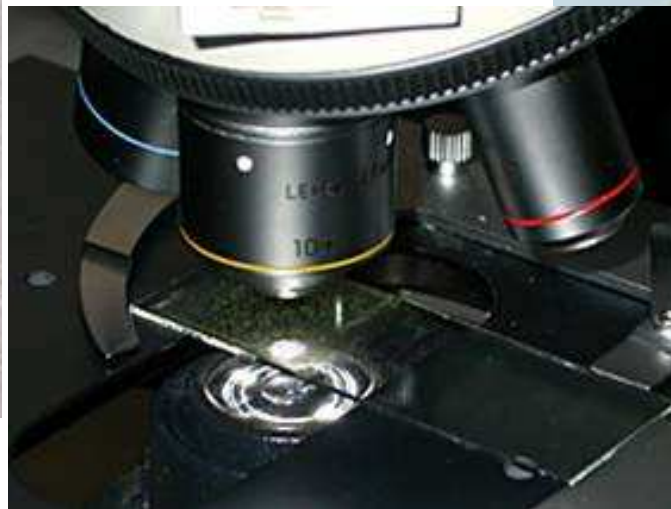
Stool examination:

Larvae output is intermittent.

75% of patients who had *Strongyloides* in one stool examination, had negative results in next four samples although they had not received any treatment.

(Dreyer, JCM 1996)

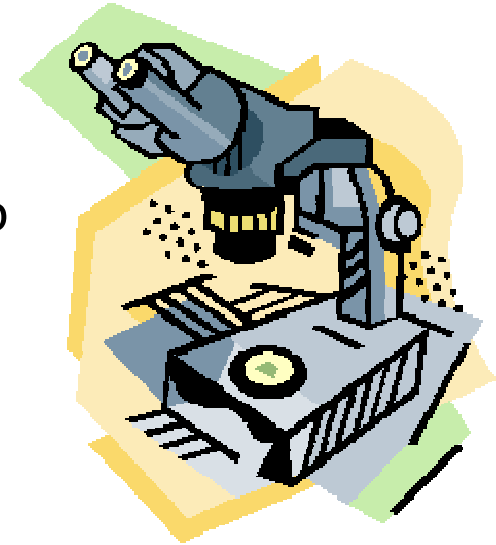
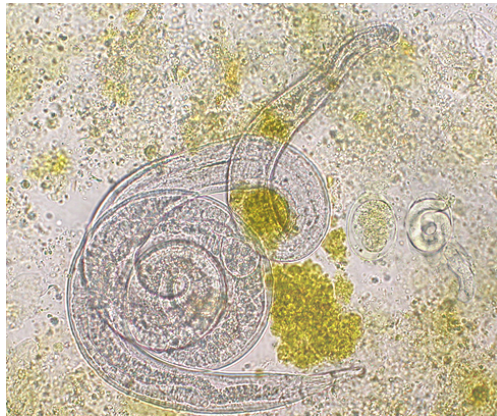
Coproparassitologico



Direct methods

Direct faecal smear examination (DS)

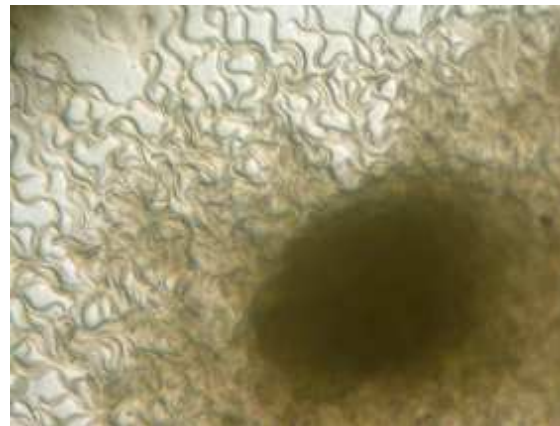
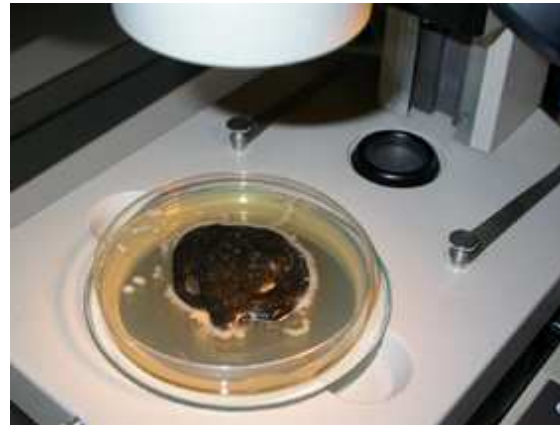
✓ Easy, inexpensive but a single examination fails to detect *at least* 70% of cases (Siddiqui A et al Clin Infect Dis. 2001)



Concentration techniques (Ritchie, Baermann, etc) and **culture**: improve sensitivity (but still far from 100%)



Coltura su agar





ELISA

- ✓ Crude antigen: *S.stercoralis*, *S.venezuelensis*, *S.ratti*. (2 commercial kits)
- ✓ Recombinant antigen: NIE.
 - Less cross-reactivity with other nematode infections
- ✓ Sensitivity ranging from 73-100%
- ✓ Immunosuppressed patients, sensitivity lower (a reduction of antibody production)
- ✓ Serology is less sensitive in returning travelers.
- ✓ Cross reaction with other nematode infections (filarial infections)
- ✓ Preincubation with *O. gutturosa* extract aimed at reducing the false positives.

Requena-Mendez A et al. The laboratory diagnosis and follow up of strongyloidiasis: a systematic review. PLoS Negl Trop Dis 2013; 7(1): e2002. Epub 2013 Jan 17.

IFAT, CTD



Immune fluorescent Antibody Test (CTD Negrar): sensitivity > 97% & specificity > 98% at titre $\geq 1:20$

Titre tends to decline within a few months of effective treatment: ideal for inclusion in trials

Boscolo M, et al. Evaluation of an Indirect Immunofluorescence Assay for Strongyloidiasis as a Tool for Diagnosis and Follow-up. *Clin Vac Immunol* 2007

Other tests

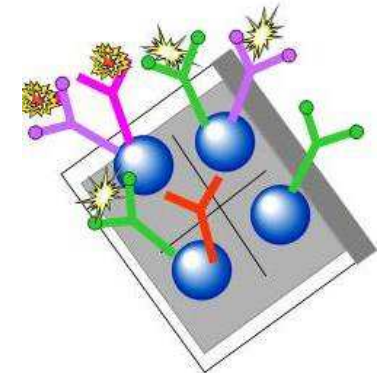
Coproantigen detection

✓ ELISA able to capture *S.stercoralis* coproantigen from infected patients without cross-reactions with other trematodes or nematodes. More studies are required

Real time PCR techniques

Specificity: 100%.

Sensitivity: not improving the Baerman, APC.



LIPS:

- Sensitivity (97%) Specificity (100%) compared to a NIE-ELISA test and to crude-ELISA

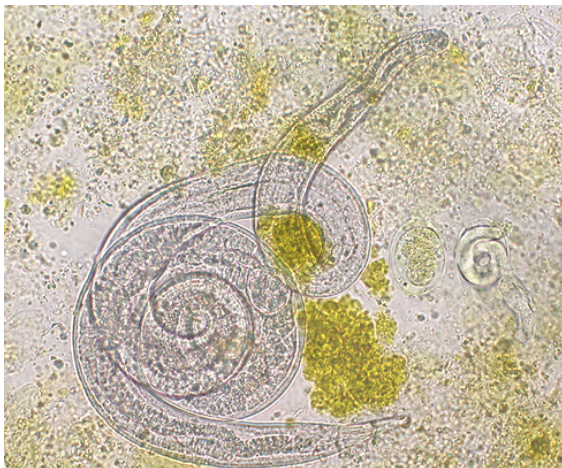
- Treatment follow-up: a reversion from positive to negative result was found more frequently (58%) compared to NIE-ELISA test (17%)

Riassumendo...

Tuttora assente una metodica *gold standard*.

Le **metodiche dirette** hanno una **bassa sensibilità** per l'escrezione irregolare o scarsa di larve.

Da valutare le tecniche sierologiche per il monitoraggio post terapia



Comparison of diagnostic accuracy of serodiagnostic tests for Strongyloidiasis

Retrospective study in collaboration with:

National Institute of Allergy and Infectious Diseases (**NIAID-NIH**)
- *Bethesda* (USA)



University of Salta - *Argentina*.



Sensitivity and specificity of serologic methods (COHEMI retrospective study on 399 cryo preserved serum samples)

test	All groups	
	Sensitivity	Specificity
NIE-ELISA	69,23	86,62
NIE-LIPS	83,85	99,63
IFAT	94,62	87,36
IVD-ELISA*	92,31	97,4
Bordier-ELISA*	90,77	94,05

* Commercially available

Recent Peruvian study in the Amazonian basin

S. stercoralis prevalence was:

0% with Kato-Katz

16% with spontaneous sedimentation in tube
technique

22% with Agar plate culture



Machicado JD, Marcos LA, Tello R, Canales M, Terashima A, et al. (2012).

Diagnosis of soil-transmitted helminthiasis in an Amazonic community of Peru using multiple diagnostic techniques. Trans R Soc Trop Med Hyg 106: 333-339.



Prevalence of strongyloidiasis in Latin America - Review

Centro Malattie Tropicali



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Centre for Tropical Diseases



- Websearch: PubMed, Scielo, BVS.
- Grey literature
- Papers published since 1991 to 2011
- Spanish, English, Italian, French and Portuguese





Prevalencia

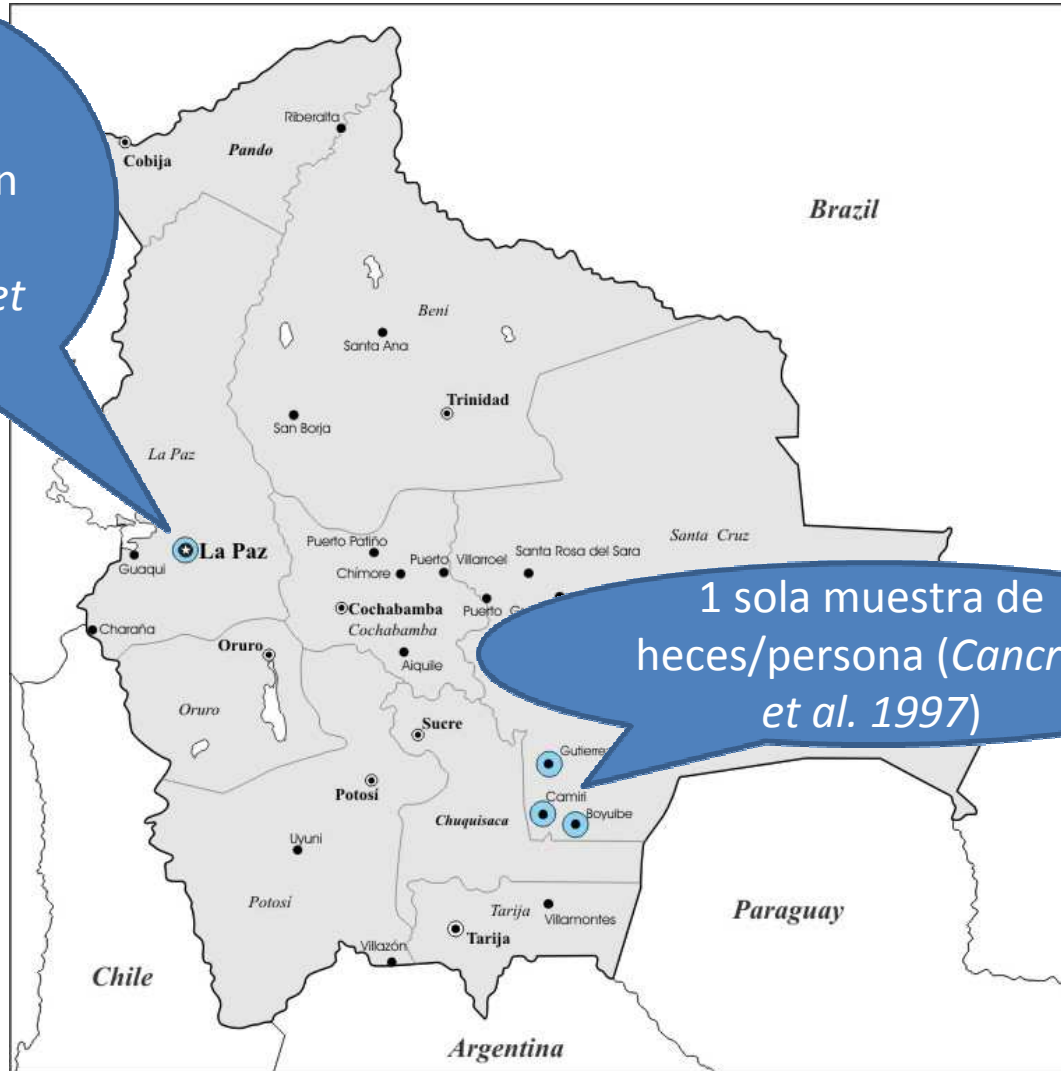
● < 5%

● = 5-10%

● = 10-20%

● > 20%

Realizado en
adultos
mayores en un
unico hogar
(Muñoz Ortiz et
al 2007)



1 sola muestra de
heces/persona (Cancrini
et al. 1997)



Seroprevalencia de *Strongyloides stercoralis* en una comunidad de Bolivianos residentes en la provincia de Bergamo, Italia

Pacientes	Screened	Positive
Varones	279	53 (18.9%)
Mujeres	754	115 (15.3%)
Totale	1033	168 (16.3%)

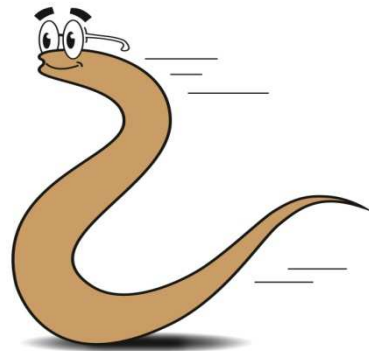


Department	N (%)	Pos (%)
Beni	13 (1,3%)	1 (7,7%)
Chuquisaca	64 (6,2%)	5 (7,8%)
Cochabamba	634 (61,5%)	96 (15,1%)
La Paz	50 (4,8%)	7 (14%)
Oruro	35 (3,4%)	6 (17,1%)
Pando	5 (0,5%)	0 (0%)
Potosì	25 (2,4%)	5 (20%)
Santa Cruz	188 (18,2%)	47 (25%)
Sucre	2 (0,2%)	0 (0%)
Tarija	15 (1,5%)	1 (6,7%)

Angheben A, Buonfrate D, Gobbi F, Anselmi M, Tais S, Postiglione C, Degani M, Gobbo M and Bisoffi Z. II Congreso Andino de Infectología, Cochabamba, 22 -24/08/2012



Dove abbiamo incontrato lo
Strongyloides?





Europa dell'est...









Non manca qualcosa...?



MAP OF AUSTRALIA WHERE STRONGYLOIDIASIS IS ENDEMIC



**5th National Workshop on Strongyloidiasis –
National Strongyloides Working Group**



KEY POINTS

For many countries there's lack of reliable data

Heterogeneity of studies for diagnostic methods,
population

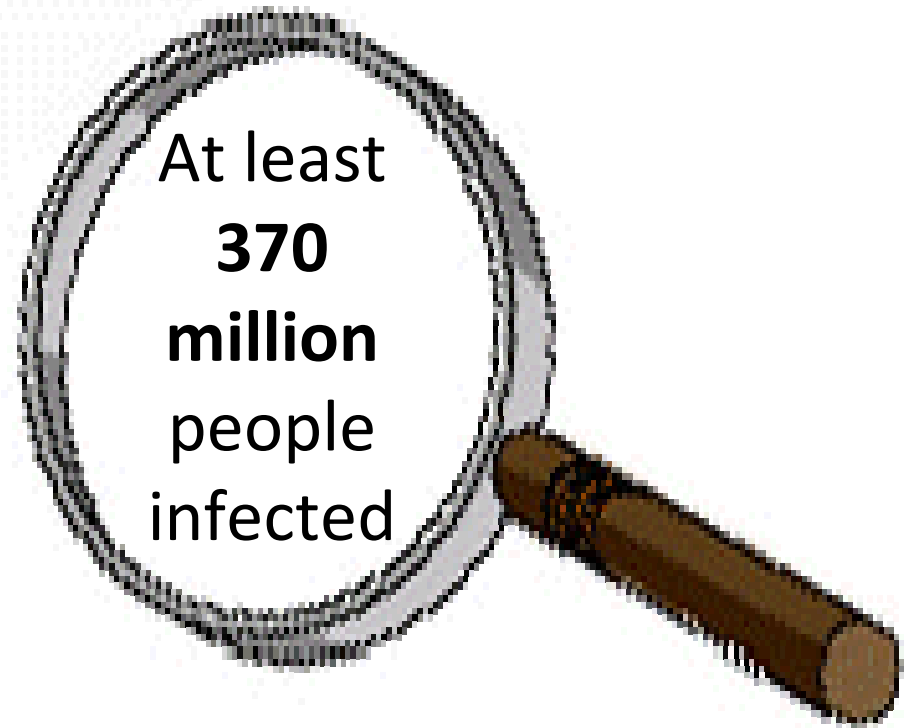
More data needed

**Need of standardized methods to perform the surveys
(study design, population, diagnostic tools)**

***Strongyloides stercoralis*: a plea for action**



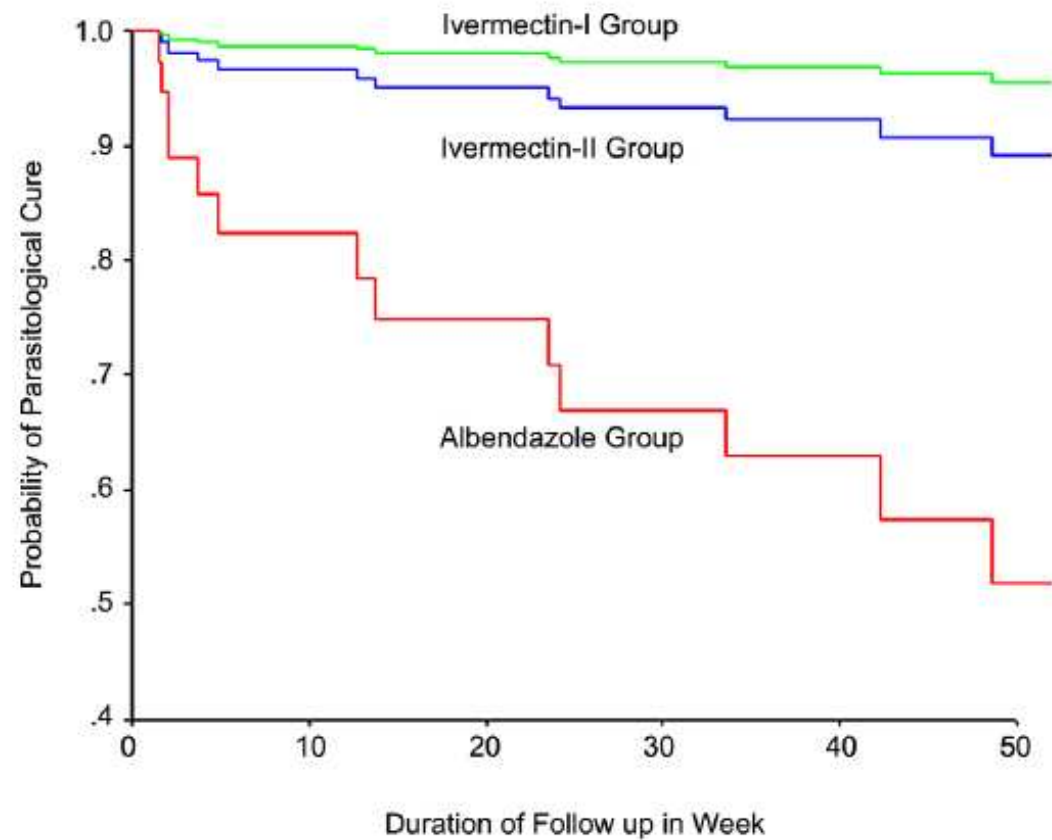
~~Some 30–100 million people are
estimated to be infected
worldwide
(probably an underestimate)”~~



At least
370
million
people
infected

Trattamento

Ivermectin vs albendazole



Suputtamongkol Y et al. [Efficacy and safety of single and double doses of ivermectin versus 7-day high dose albendazole for chronic strongyloidiasis](#). PLoS Negl Trop Dis. 2011 May 10;5(5):e1044.

Randomized Clinical Trial on Ivermectin versus Thiabendazole for the Treatment of Strongyloidiasis

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Table 4 - Outcome at follow-up (month 3rd-6th) in the two arms (92 patients with IFAT titer ≥ 80)

Measures of efficacy	<i>Ivermectin</i>	<i>Thiabendazole</i>	<i>p</i>
All criteria fulfilled	32/47 (68.1%)	31/45 (68.9%)	0.93
Patients with partial response ¹ included	41/47 (87.2%)	40/45 (88.9%)	0.81
Efficacy based on negativization of direct tests	22/24 (91.7%)	27/27 (100%)	0.22 [^]

Toxicity

Table 5 – Side effects (analysis on all 223 patients included in trial)

Side effects	<i>Ivermectin</i>	<i>Thiabendazole</i>	<i>p</i>
Grade 1	19/115 (16.5%)	36/108 (33.3%)	0.01
Grade 2	5/115 (4.3%)	43/108 (39.8%)	0.00
All	24/115 (20.9%)	79/108 (73.1%)	0.00

Riassumendo...



Ivermectina farmaco di elezione



Albendazolo: efficacia non sufficiente

Therapy: ok ivermectin...

But how many doses?

WHO
MODEL
FORMULARY

2008

Strongyloidiasis

Strongyloidiasis is an infection of the small intestine caused by *Strongyloides stercoralis*. All infected patients should be treated. Ivermectin (section 6.1.2) in a single dose of 200 micrograms/kg **or** 200 micrograms/kg/day on 2 consecutive days is the treatment of choice for chronic strongyloidiasis but it may not be available in all countries. **Albendazole**, 400 mg once or twice daily



STRONG TREAT 1 to 4

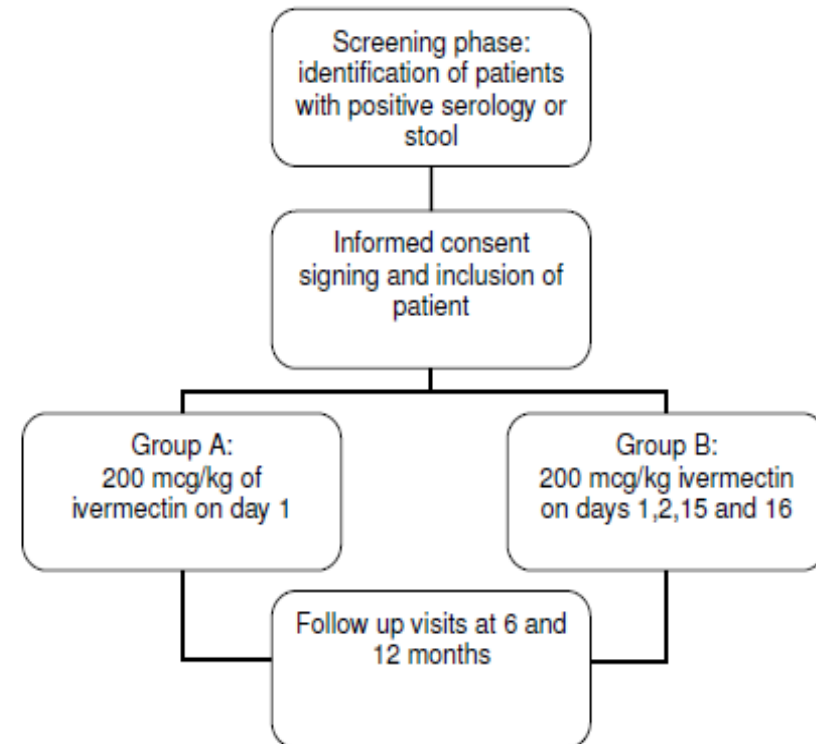
**Randomized, Open-label, Multi Centre
Phase III Clinical Trial on Multiple versus
Single Dose of Ivermectin for the
Treatment of Strongyloidiasis**

Protocol rev.3

By Dora Buonfrate and Zeno Bisoffi

24th February 2012

STRONG TREAT 1 to 4. 24th February 2012



The most neglected...

Grand Challenges
in Global Health



March 2013

Solutions for onchocerciasis, lymphatic filariasis, soil-transmitted helminth infections (ascariasis, trichuriasis, and hookworm disease), and schistosomiasis

Riflessioni finali...

- Essenziali ulteriori ricerche sui metodi diagnostici
- Linee guida – protocolli che definiscano le categorie “a rischio” per le quali eseguire uno screening

Screening

1. Transplant candidates
2. Oncology patients
3. Known HTLV1 (HIV?) patients
4. Any subject with eosinophilia
5. Immigrants (with or without eosinophilia)
6. Any candidate for any reason to corticosteroids and/or immune suppressants (+ biologicals??)

Is it justified, in these groups, to treat negatives, too??

Should systematic treatment replace serology? (C/E studies needed)