IMMi

European Confederation of Medical Mycology
ECMM
Center of Excellence in Clinical and Laboratory Mycology and Clinical Studies

Universitätsmedizin Essen
Universitätsklinikum

Mikrobiologie, Diagnostik und Pathomechanismen

von *Pneumocystis jirovecii*

Peter-Michael Rath

Institut für Med. Mikrobiologie

Conflicts on interest: None

Geschichte

1909	Chagas	Meerschweinchenlunge (Trypanosoma)
1912	Carini	Rattenlunge (Trypanosoma)
1912	Delanoë & Delanoë	Rattenlunge (gesund) *Pneumocystis carinii*
1942	Van der Meer & Brug	Erwachsene
1951	Vanek & Jirovec	Kinder („Plasma cell pneumonia“)
1970	Vavra & Kucera	Pilz ! Zyste ist Ascospore
1976	Frenkel	*P. jiroveci* (Zoologische Nomenklatur)
1988	Edman, Kovacs et al	Pilz ! 16s-RNA
1989	Stringer & Stringer	Pilz ! cDNA
1999	Frenkel	*P. jiroveci* (Botanische Nomenklatur)
2002	Stringer	*P. jiroveci*
2009	Stringer	*P. jirovecii*

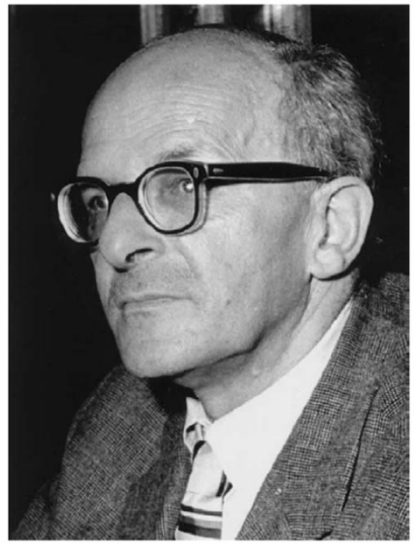
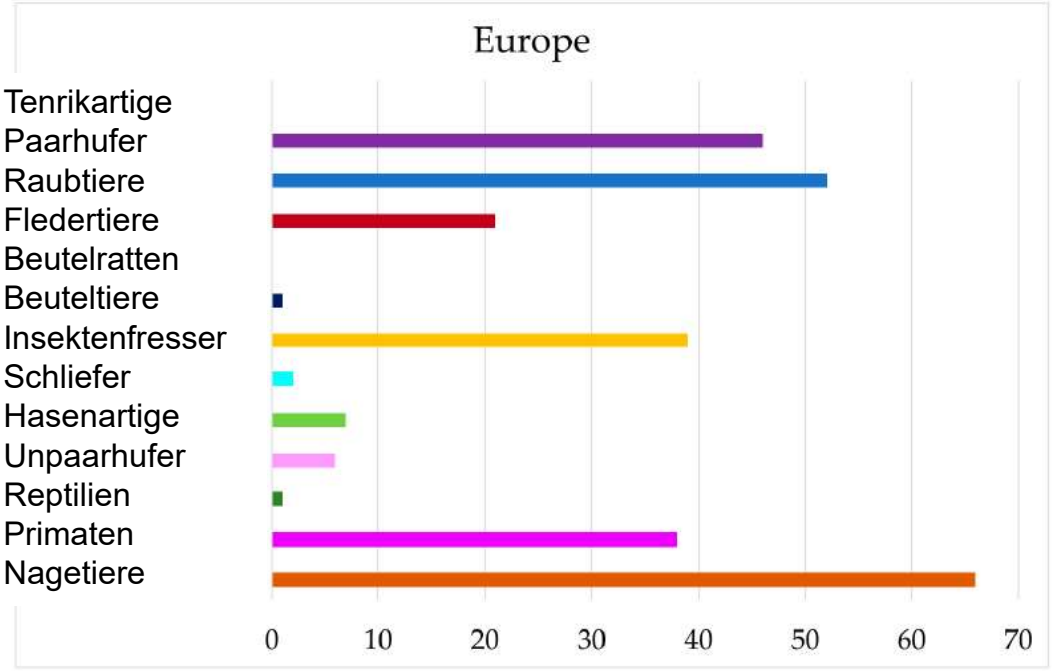


Figure 1. Otto Jirovec. Courtesy of the photo archives of the Department of Parasitology, Faculty of Science, Charles University, Prague, Czech Republic.

Pneumocystis bei Tieren

Anzahl der publizierten Untersuchungen



Prävalenz

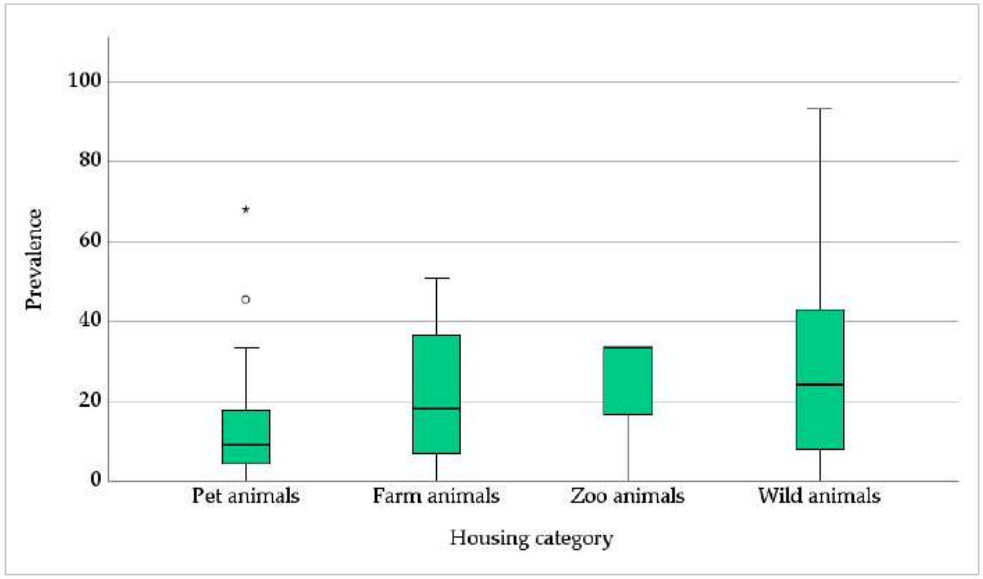


Figure 5. Boxplot of *Pneumocystis* prevalence in different housing categories (rings and asterisks represent mild and extreme outliers, ○ = values between inner and outer fence [1.5-fold interquartile range], * = values beyond outer fence [3-fold interquartile range]).

Article
Meta-Analysis and Systematic Literature Review of the Genus *Pneumocystis* in Pet, Farm, Zoo, and Wild Mammal Species
Christiane Weissenbacher-Lang *, Anna Grenl and Barbara Blasi

Journal of *Fungi*

Fungi **2023**, *9*, 1081. https://doi.org/10.3390/jof9111081

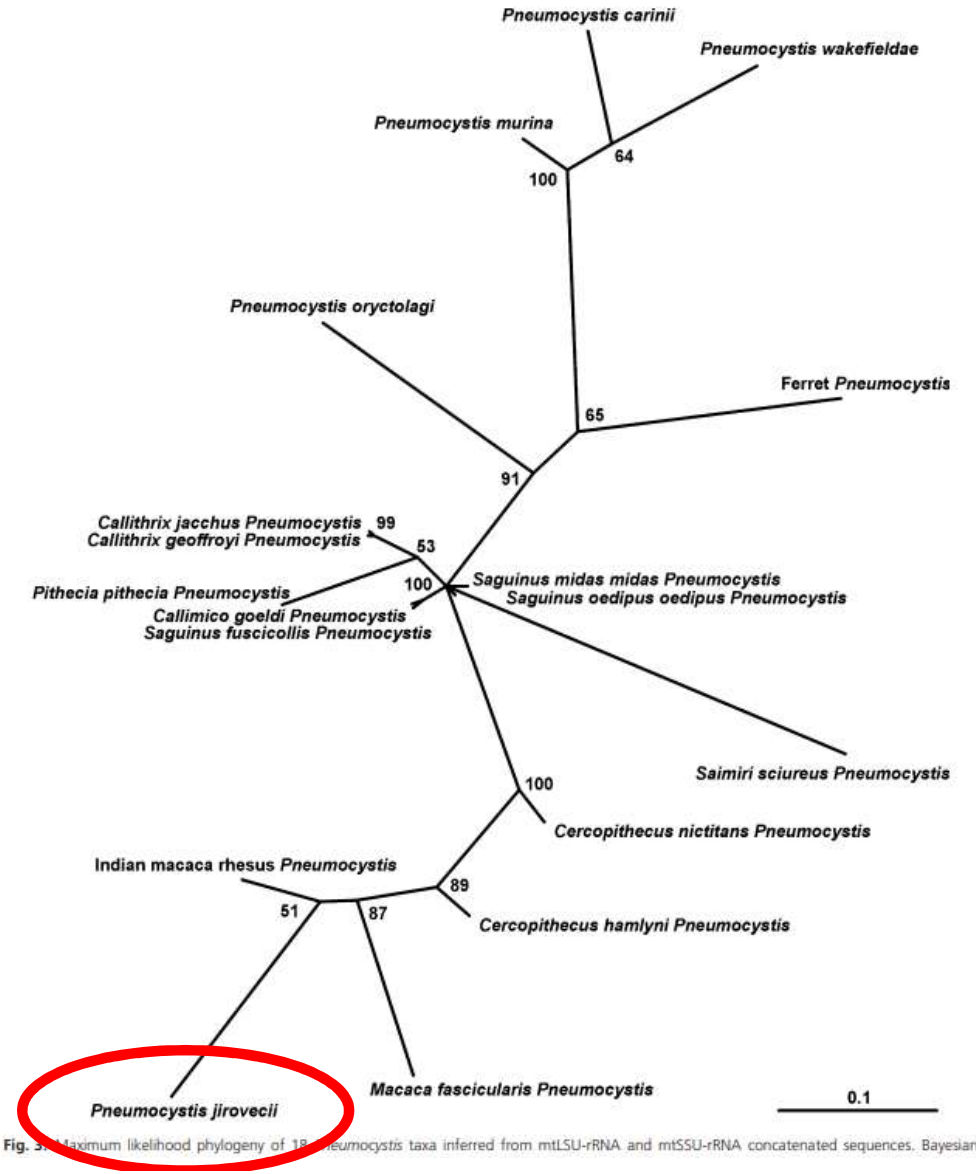


Fig. 3. Maximum likelihood phylogeny of 18 *Pneumocystis* taxa inferred from mtLSU-rRNA and mtSSU-rRNA concatenated sequences. Bayesian

 DOI:10.1111/j.1574-6976.2006.00037.x

Pneumocystis ist ein stenoxener Erreger

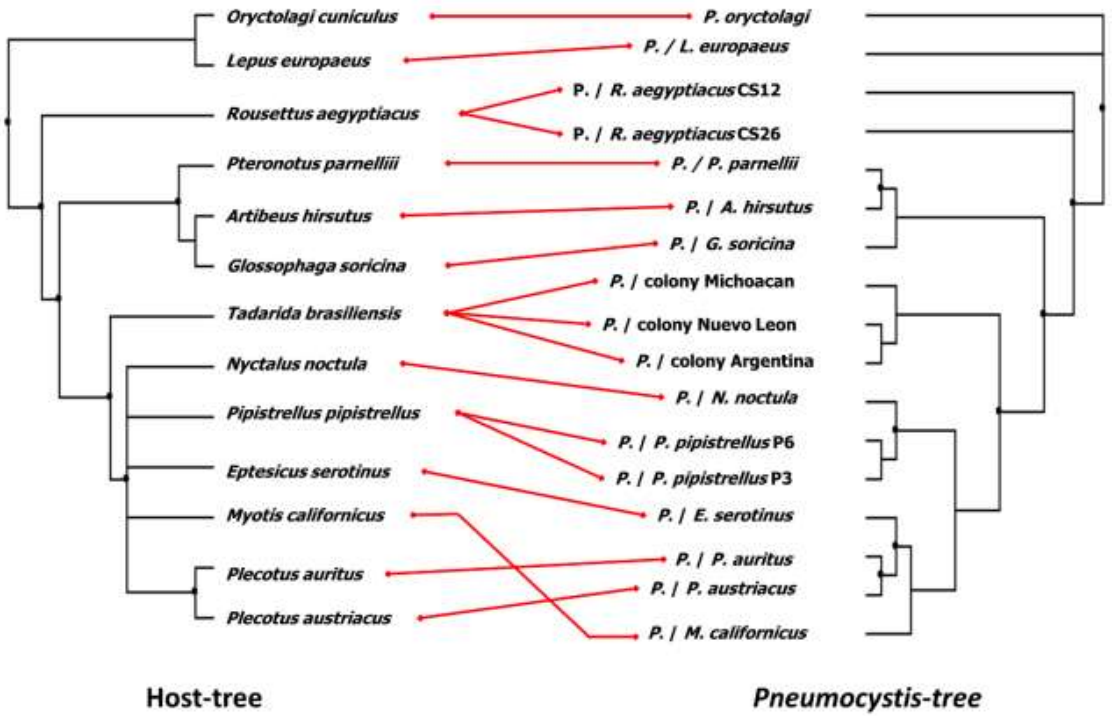
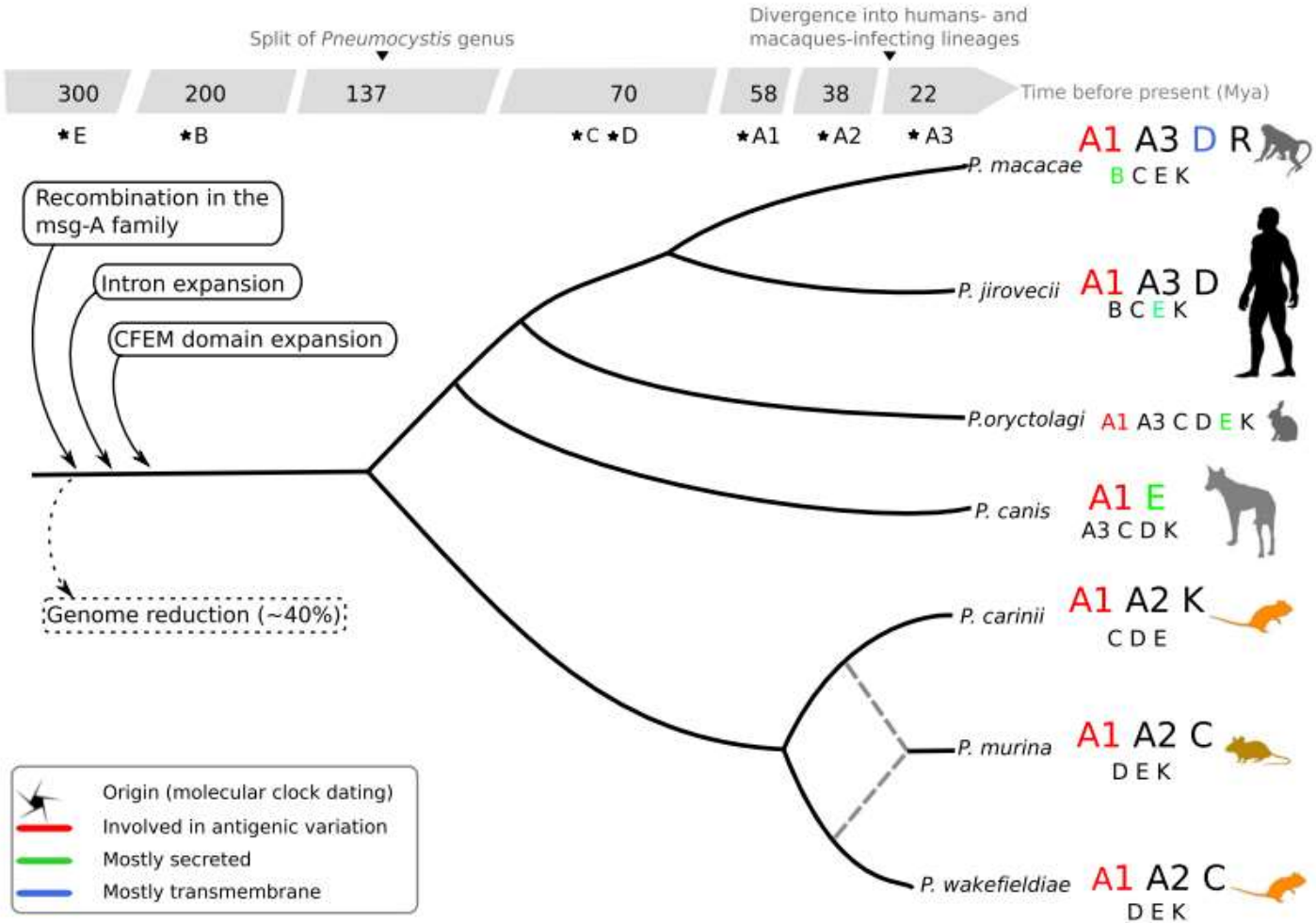


Figure 3 Parallel phylogenies of *Pneumocystis* mtSSU rRNA sequences and their bat hosts (from Derouiche *et al.*, 2009).

Christine Demanche [1], Jacques Guillot [2], Magali Chabé [1,*]

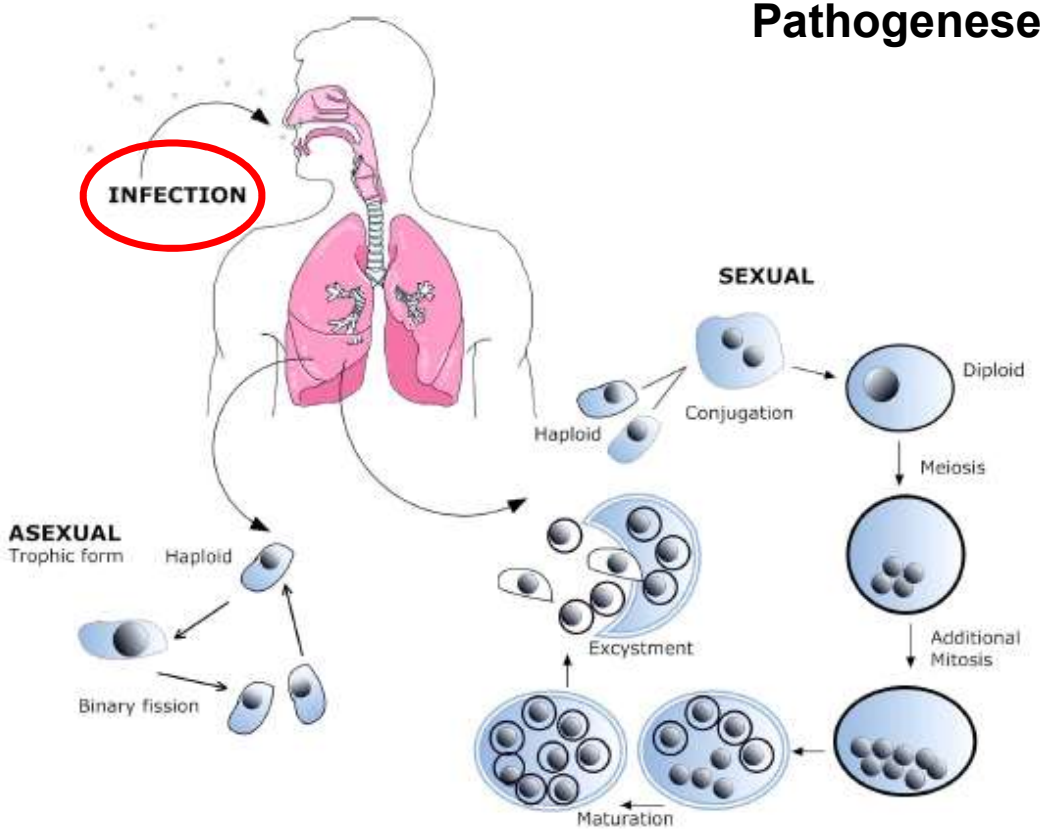
OBM Genetics
2019, volume 3, issue 2
doi:10.21926/obm.genet.190207

Evolution von *Pneumocystis*



COMMUNICATIONS BIOLOGY | (2021)4:305 | https://doi.org/10.1038/s42003-021-01799-7 | www.nature.com/commsbio

Pathogenese



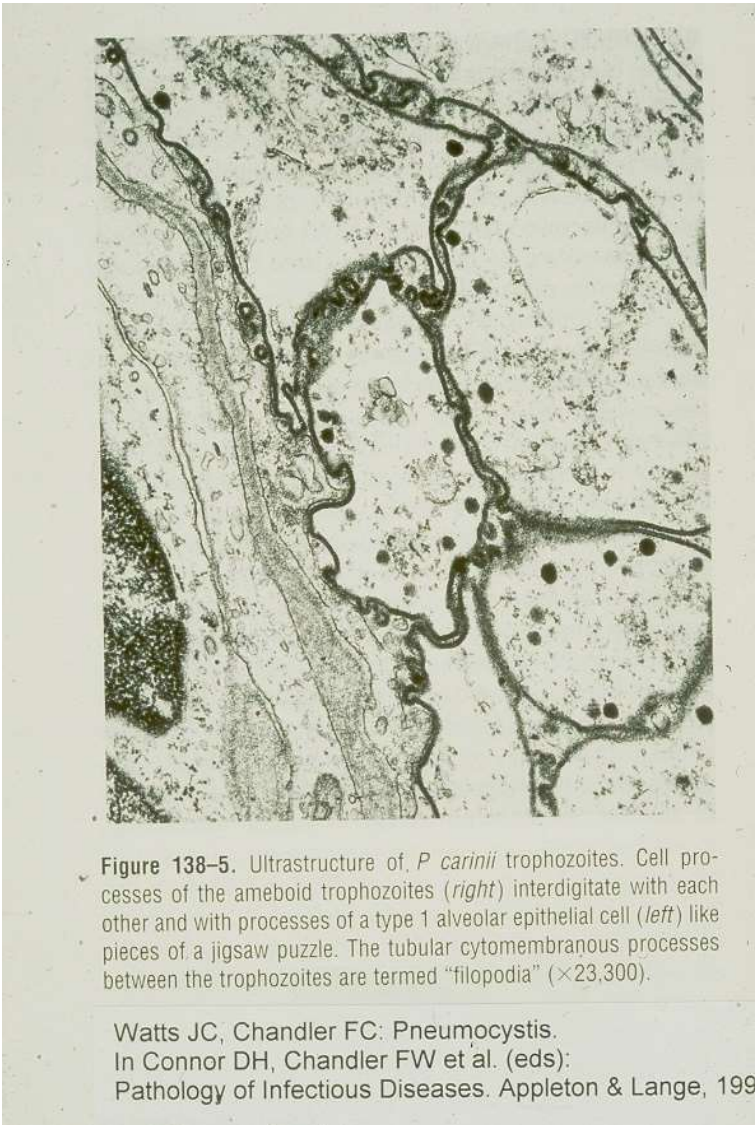


Figure 138–5. Ultrastructure of *P carinii* trophozoites. Cell processes of the ameboid trophozoites (*right*) interdigitate with each other and with processes of a type 1 alveolar epithelial cell (*left*) like pieces of a jigsaw puzzle. The tubular cytomembranous processes between the trophozoites are termed "filopodia" (×23,300).

Watts JC, Chandler FC: Pneumocystis.
In Connor DH, Chandler FW et al. (eds):
Pathology of Infectious Diseases. Appleton & Lange, 199

- **Diffusionsstörung durch Trophozoite und Zysten in Matrix.**
- **(1-3)-ß-D-Glukan (nur Zysten) aktiviert Alveolarmakrophagen (Mediatoren).**
- **Neutrophile und CD8+T-Zellen verursachen Alveolarschaden.**

Beck JM & Cushion MT: Eucaryotic Cell 8 (2009): 446-460

An Outbreak of *Pneumocystis jiroveci* Pneumonia with 1 Predominant Genotype among Renal Transplant Recipients: Interhuman Transmission or a Common Environmental Source?

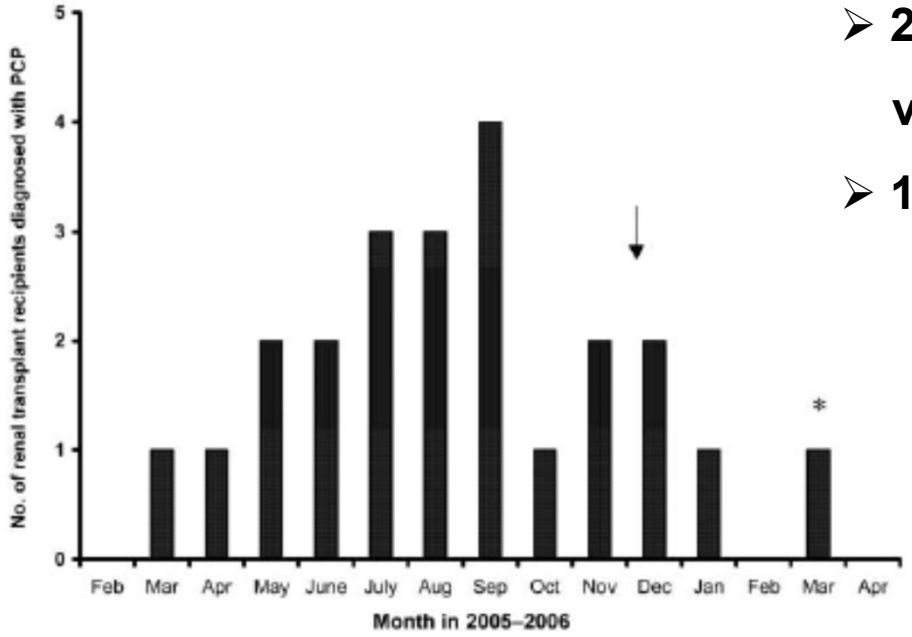


Figure 1. Number of renal transplant recipients with confirmed *Pneumocystis jiroveci* pneumonia (PCP) during 2005–2006, by month. *The first new case reported after 1 February 2006. *Arrow,* start of antibiotic prophylaxis for PCP.

Clinical Infectious Diseases 2007;44:1143–9

- **22 Nieren-transplantierte Patient*innen innerhalb von 11 Monaten**
- **1 Genotyp bei 12 / 16 Patienten**

Epidemiological Outbreaks of *Pneumocystis jirovecii* Pneumonia Are Not Limited to Kidney Transplant Recipients: Genotyping Confirms Common Source of Transmission in a Liver Transplantation Unit

Journal of Clinical Microbiology

May 2016 Volume 54 Number 5

Aktueller: Clinical Infectious Diseases® 2022;74(4):639–47

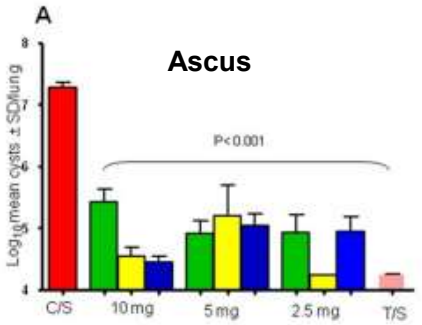
Echinocandin Treatment of *Pneumocystis* Pneumonia in Rodent Models Depletes Cysts Leaving Trophic Burdens That Cannot Transmit the Infection

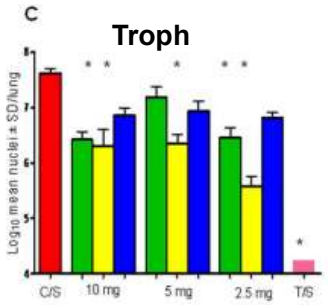
Melanie T. Cushion[1,2]*, Michael J. Linke[2], Alan Ashbaugh[1,2], Tom Sesterhenn[1,2], Margaret S. Collins[1,2]

PLoS ONE | www.plosone.org 1 January 2010 | Volume 5 | Issue 1 | e8524

Mausexperiment

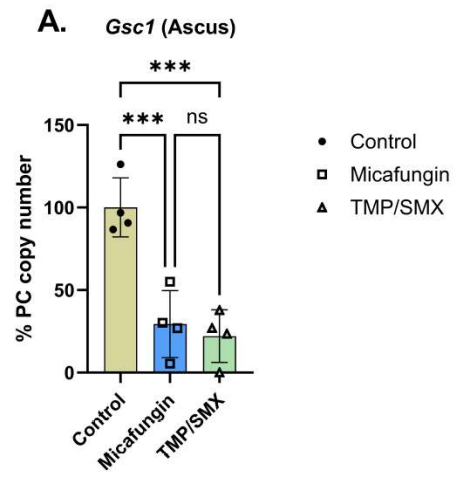
Anidulafungin
Caspofungin
Micafungin
Cotrim

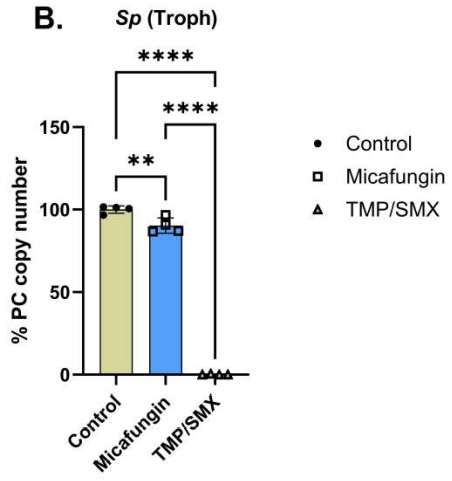




Maus Lungenpräparat

Micafungin
Cotrim





Precision-cut lung slices as an *ex vivo* model to study *Pneumocystis murina* survival and antimicrobial susceptibility

Ferris T. Munyonho,[1] Robert D. E. Clark,[1] Dong Lin,[1] Mst Shamima Khatun,[1] Dora Pungan,[1] Guixiang Dai,[1] Jay K. Kolls

New Orleans, USA

mBio January 2024 Volume 15 Issue 1 10.1128/mbio.01464-23

Pneumocystis carinii Infection: Evidence for High Prevalence in Normal and Immunosuppressed Children

Linda L. Pifer, Ph.D., Walter T. Hughes, M.D., Sergio Stagno, M.D., *and* Diane Woods, B.S.

From the Infectious Diseases Service, St. Jude Children's Research Hospital, Memphis, Tennessee, and Department of Pediatrics, University of Alabama Medical Center, Birmingham

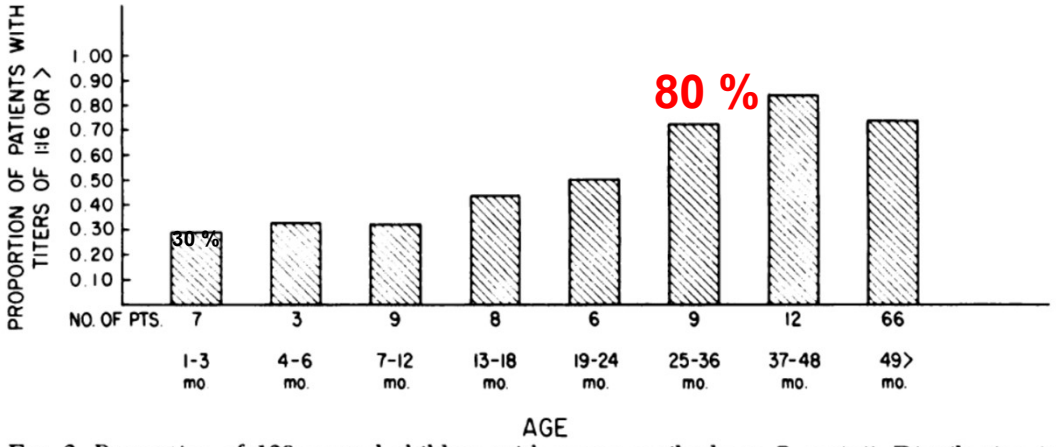


FIG. 2. Proportion of 120 normal children with serum antibody to *P. carinii*. Distribution is according to age, and bars represent proportion (percentage) of patients tested with titers of 1:16 or greater, determined by IFA.

High seroprevalence of *Pneumocystis* infection in Spanish children

N. Respaldiza[1], F. J. Medrano[2], A. C. Medrano[3], J. M. Varela[2], C. de la Horra[1], M. Montes-Cano[1], S. Ferrer[4], I. Wichmann[1], D. Gargallo-Viola[4] and E. J. Calderon[2]

Table 1. Seroprevalence of *Pneumocystis* infection in healthy Spanish children by age, gender and place of residence

	No. tested	No. (%) with positive immunoblot	p[a]
Age (years)			
6	23	12 (52.1)	< 0.001
10	82	54 (65.8)	
13	128	103 (80.4)	
Sex			
Male	125	88 (70.4)	0.47
Female	108	81 (75)	
Place of residence			
Coronil	127	88 (69.3)	0.35
Palmar	70	55 (78.5)	
Pruna	36	26 (72.2)	

[a]Chi-square test.

Pediatrics 1978;61;35

Pneumocystis Colonization Is Highly Prevalent in the Autopsied Lungs of the General Population

Carolina A. Ponce,[1] Myriam Gallo,[2] Rebeca Bustamante,[1] and Sergio L. Vargas[1]

[1]Programa de Microbiología y Micología, Instituto de Ciencias Biomédicas, Facultad de Medicina Universidad de Chile, and [2]Servicio Médico Legal, Santiago, Chile

Clinical Infectious Diseases 2010;50:347–53

Table 1. Autopsy Results and *Pneumocystis* Status, as Determined by Nested Polymerase Chain Reaction DNA Amplification and, in Addition, by Immunofluorescent Analysis for Those Who Died of a Violent Cause

Circumstance of death	Total no.	Age, median years (range)	Positive for *Pneumocystis*,[a] no. (%)
Violent death	55	…	34 (61.8)
Traffic accident	22	37.9 (12.7–66.6)	13 (59.0)
Suicide	20	42.7 (6.0–88.0)	13 (65.0)
Homicide	10	41.5 (23.6–50.1)	7 (70.0)
Other[b]	3	22.1 (10.0–68.3)	1 (NA)
Nonviolent death (medical diagnosis)[c]	19	60.1 (5.1–82.5)	15 (78.9)
Undetermined	3	55.0 (44.1–55.2)	1 (NA)
Total	77	…	50 (64.9)

PCR positiv ~ 65 %

Risiko-Erkrankungen und Medikamente

TABLE 4 | Risk category for *Pneumocystis* pneumonia (PcP) in HIV-negative patients, Spain, 2008–2012.

Risk category	No. (%)
Hematologic malignances	349 (29)
Chronic lung diseases	192 (15.9)
Malignances other than hematologic	179 (14.9)
Autoimmune diseases*	93 (7.7)
Chronic nephropathies	68 (5.6)
Treatment with chemotherapy	59 (5)
Any transplant	54 (4.5)
Hematologic disorders other than malignances	21 (1.7)
Chronic liver diseases	14 (1.2)
Unknown	176 (14.5)

**Rheumatoid arthritis, systemic lupus erythematosus, polymyositis, dermatomyositis, chronic mixed connective tissue disease, Crohn's disease, and systemic vasculitis.*

Table 1
Drugs predisposing to *Pneumocystis jirovecii* pneumonia

Therapeutic principle	Drug
Anti-CD20 monoclonal antibody	Rituximab Obinutuzumab Ofatumumab
Chemotherapy	Fludarabine Methotrexate Cyclophosphamide Temozolomide
mTOR inhibition	Temsirolimus Everolimus
Calcineurin inhibition	Cyclosporin Tacrolimus
Phosphatidylinositol 3-kinase inhibition	Idelalisib
Tyrosine kinase inhibition	Ibrutinib
Biological agents	Alemtuzumab Infliximab
Anti-CCR-4 antibody	Mogamulizumab
Anti-SLAMF	Elotuzumab
JAK inhibition	Ruxolitinib etc.
Checkpoint inhibition	Nivolumab, etc.

Pneumocystis jirovecii colonization in Chronic Obstructive Pulmonary Disease (COPD)

Khodavaisy S[1, 2], Mortaz E[3], Mohammadi F[2], Aliyali M[4], Fakhim H[5], Badali H[6]*

Table 1. *P. jirovecii* colonization in COPD patients

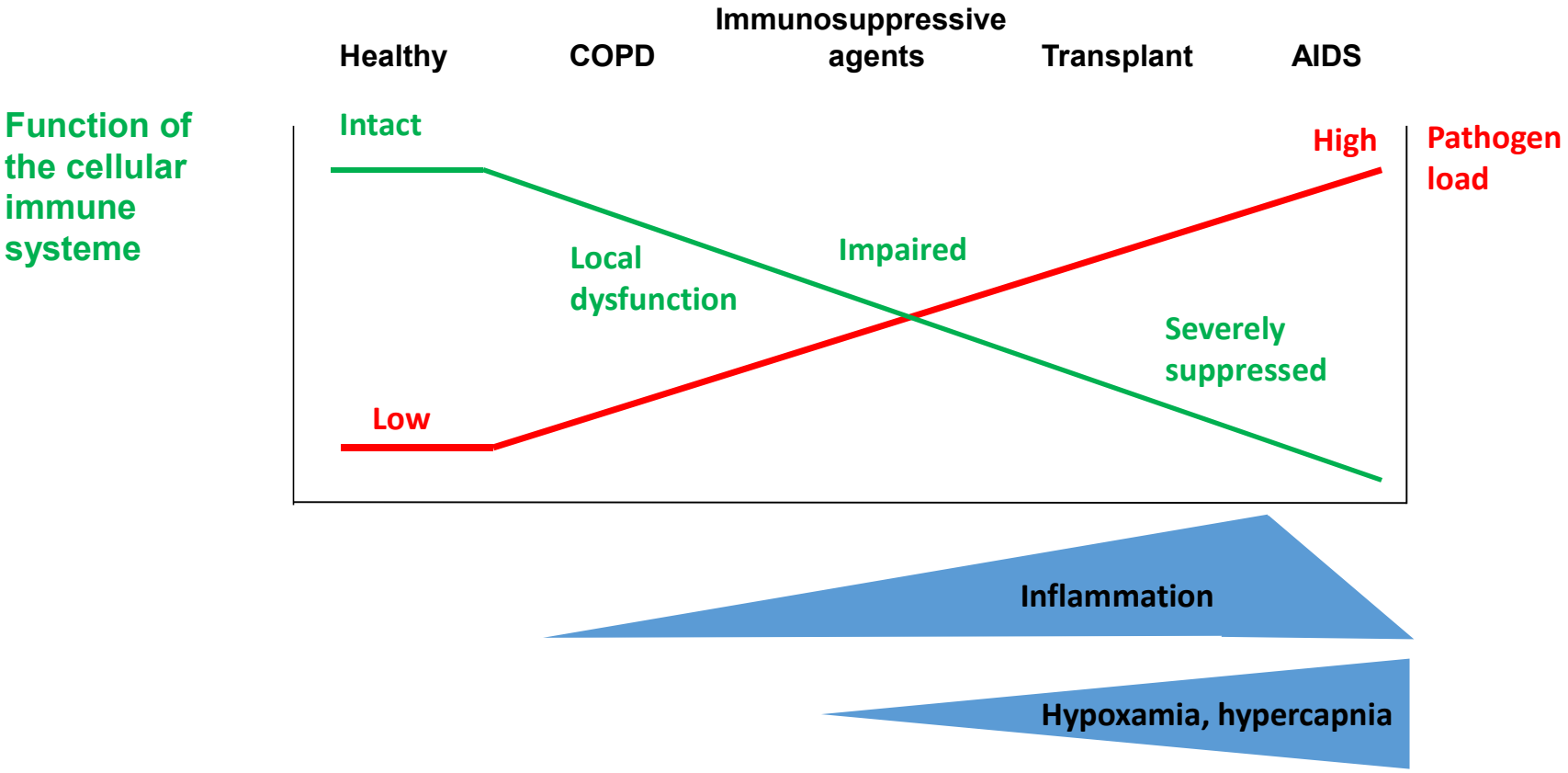
Patients, no.	Diagnostic Sample	Diagnostic Methods	Population	% Colonization	References
50	sputum	IHC stains, IF stains	Patients with chronic bronchial disease	10.0%	[10]
8	BAL	Nested PCR	Patients with COPD	37.5%	[14]
37	BAL and sputum	Nested PCR	Patients with COPD	41%	[12]
23	BAL, sputum, and tracheal aspirates	Touch-down PCR	In-patients with suspected bacterial pneumonia and COPD	43.5%	[15]
23	BAL	Nested PCR	Patients with COPD undergoing bronchoscopy	17.5%	[16]
37	sputum	Nested PCR	Patients with chronic bronchitis	40.5%	[11]
51	Sputum	Nested PCR	COPD	54.9%	[13]
68	Lung resection	Nested PCR	COPD and other lung diseases	19.1%	[8]
50	Sputum	Nested PCR	COPD	16.0%	[17]

Abbreviation: IHC, immunohistochemical; IF, immunofluorescence; COPD, chronic obstructive pulmonary disease; PCR, polymerase chain reaction

Proinflammatorischer Effekt ?

Curr Med Mycol, 2015, 1(1): 42-48

Pathogenese

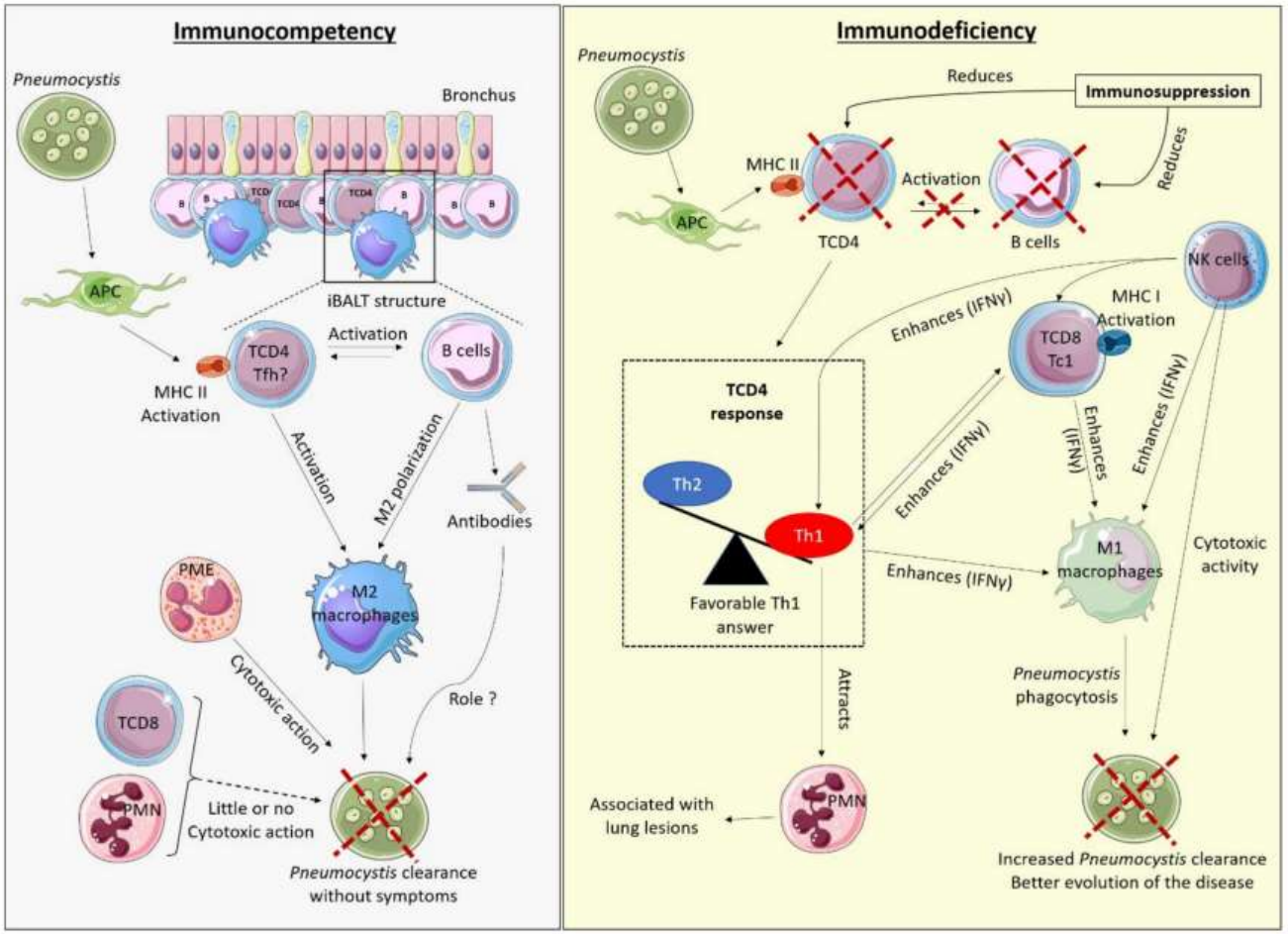


Curr Fungal Infect Rep
DOI 10.1007/s12281-014-0188-8

ADVANCES IN DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS (U BINDER, SECTION EDITOR)

Update on Diagnosis of *Pneumocystis* Pulmonary Infections

Peter-Michael Rath · Joerg Steinmann



Immune Response in *Pneumocystis* Infections According to the Host Immune System Status

Eléna Charpentier [1,2,*], Sandie Ménard [2], Catherine Marques [2], Antoine Berry [1,2] and Xavier Iriart [1,2,*]

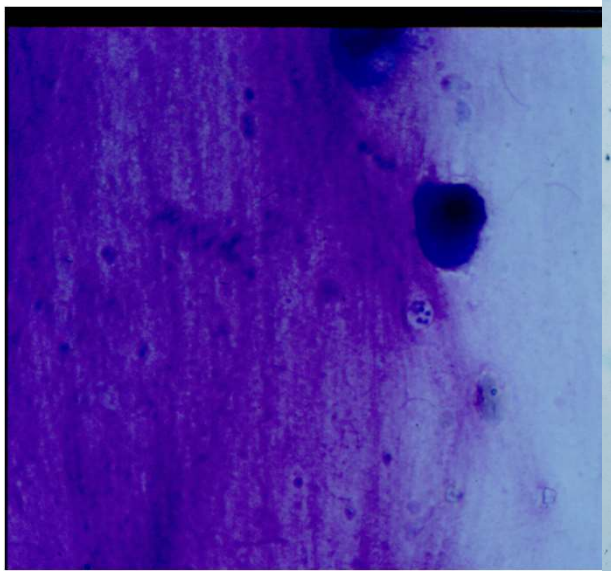
J. Fungi 2021, 7, 625. https://doi.org/10.3390/ jof7080625

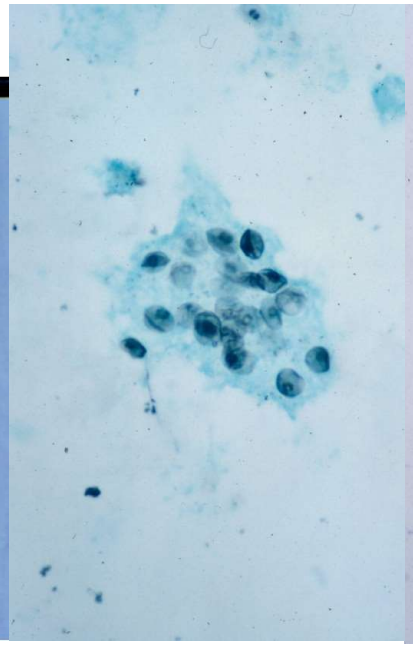
Labordiagnostik

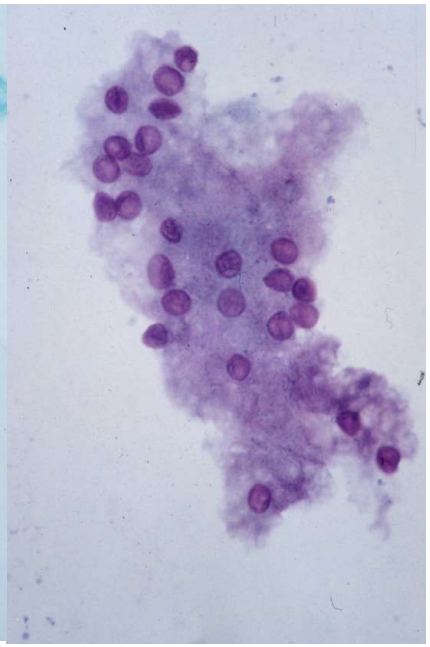
Mikroskopie: obsolet (bei non-AIDS-Patient*innen geringerer Keimload = geringere Sensitivität)

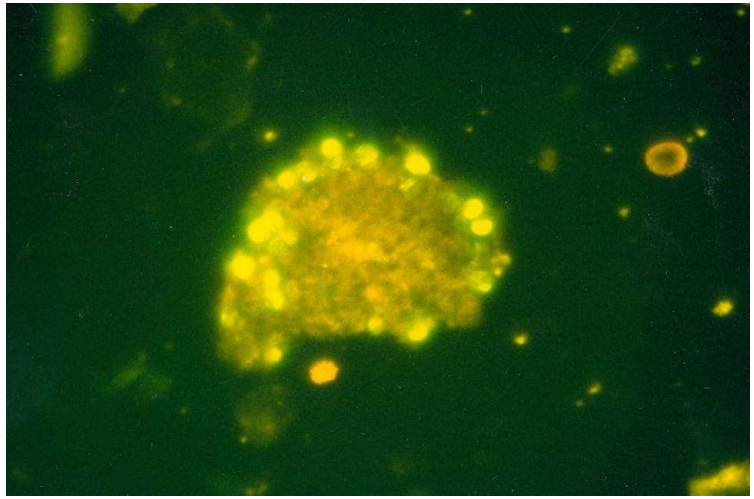
Standard: quantitative real time-PCR, LAMP

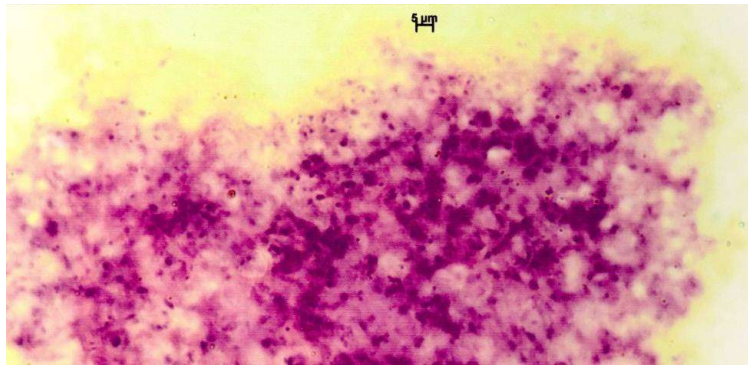
ß-1,3-D-Glukan

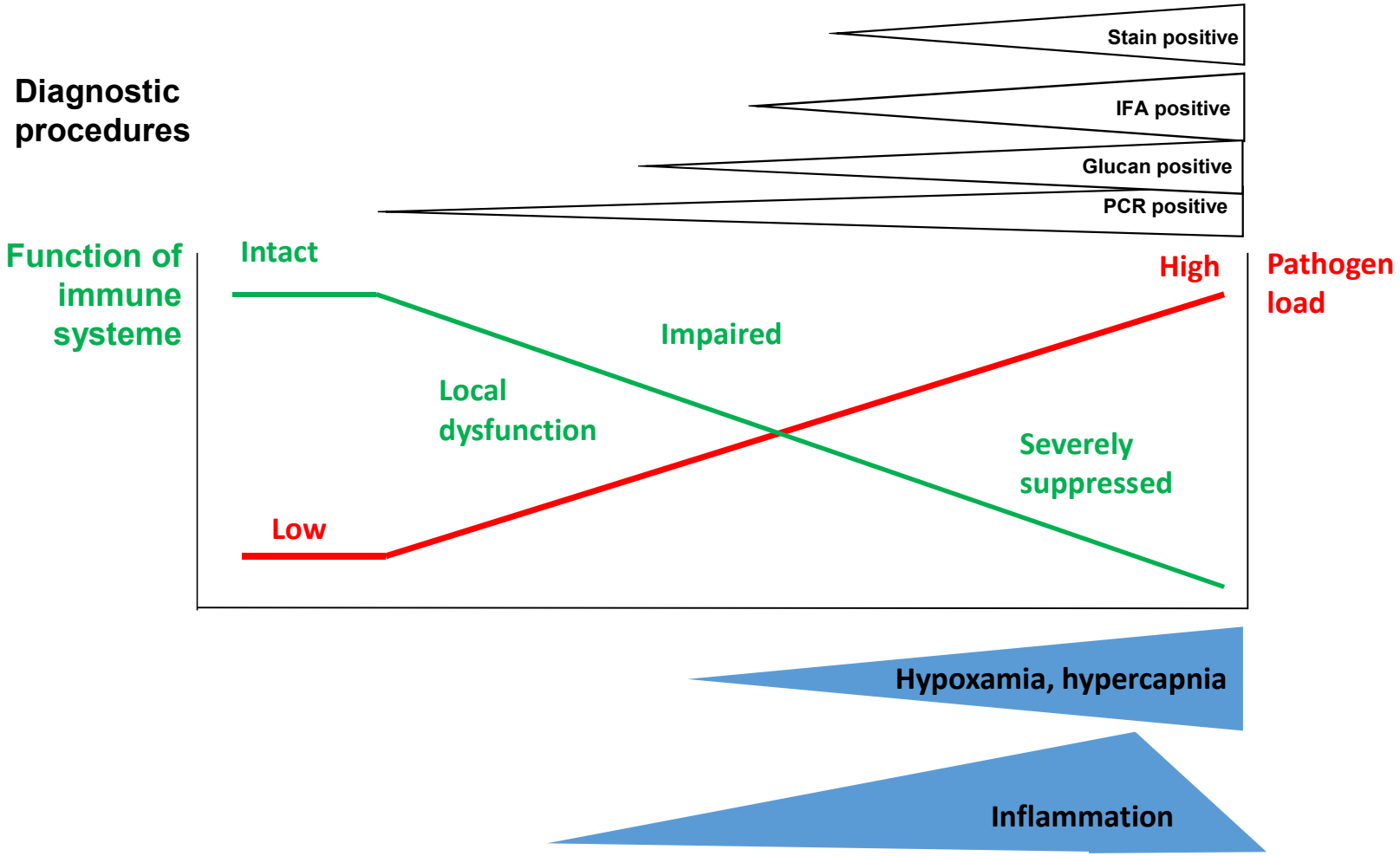












Curr Fungal Infect Rep
DOI 10.1007/s12281-014-0188-8

ADVANCES IN DIAGNOSIS OF INVASIVE FUNGAL INFECTIONS (U BINDER, SECTION EDITOR)

Update on Diagnosis of *Pneumocystis* Pulmonary Infections

Peter-Michael Rath · Joerg Steinmann

Evaluation of PCR in Bronchoalveolar Lavage Fluid for Diagnosis of *Pneumocystis jirovecii* Pneumonia: A Bivariate Meta-Analysis and Systematic Review

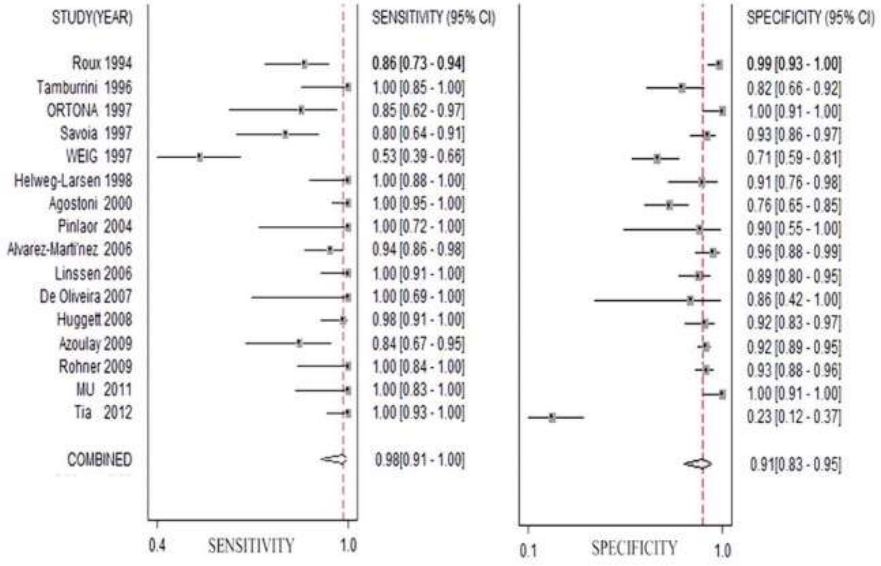
Li-Chao Fan, Hai-Wen Lu, Ke-Bin Cheng, Hui-Ping Li, Jin-Fu Xu*

Table 2. Technical details methods of the PCR in the included studies.

Study reference no.	BALF sample volume(ml)	Samle centrifugation	DAN extraction methods	PCR method	target gene	Appropriate control
15	3–5	Y	QIAamp	nested PCR	mt LSU rRNA	Y
16	0.2	Y	proteinase	conventional PCR	mt LSU rRNA	Y
17	0.5	Y	proteinase	qPCR	Kex-1	Y
18	NR	Y	QIAamp	single PCR	mt rRNA	Y
19	0.2; 0.75	NR	DNeasy, QIAamp	conventional PCR	mt LSU rRNA	Y
20	NR	Y	Wizard purification	RT-PCR	mt LSU rRNA	Y
21	0.2	Y	Qiagen	real-time PCR	DHPS	NR
22	1	NR	QIAamp	real-time PCR	DHPS	Y
23	NR	Y	phenol chloroform	single PCR	5S rRNA	Y
24	0.25	NR	phenol chloroform	nested PCR	ITS	Y
25	2	Y	phenol-chloroform/Chelex	TD-PCR	mt LSU rRNA	Y
26	NR	Y	QIA purification	nested PCR	mt LSU rRNA	Y
27	0.1	Y	proteinase K	nested PCR	mt rRNA	Y
28	NR	NR	proteinase K	single PCR	mt LSU rRNA	Y
29	1	NR	phenol-chloroform	nested PCR	mt LSU rRNA	Y
30	10	Y	phenol-chloroform	single PCR	mt rRNA	NR

Abbreviations: DHPS, dihydroperoate synthase; ITS, internal transcribed spacer; mt LSU rRNA, mitochondrial large-subunit ribosomal RNA; mt rRNA, mitochondrial ribosomal RNA; NR, not reported; qPCR, quantitative polymerase chain reaction; RT-PCR, reverse transcriptase -polymerase chain reaction; TD-PCR, a single-round touchdown PCR; Y, yes.

doi:10.1371/journal.pone.0073099.t002



Sensitivität 98 % **Spezifität 91 %**

Non-invasive diagnosis of *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis

Julien Senécal [1], Elizabeth Smyth [2], Olivier Del Corpo [1], Jimmy M. Hsu [1],

Sensitivität der PCR

Serum	**77 %**
Mundspülflüssigkeit	**77 %**
Nasopharyngealaspirat	**86 %**
Rachenabstrich	**90 % (10 AIDS-Patienten mit PcP)***
Induziertes Sputum	**99 %**

> HIV Med. 2021 Apr;22(4):321-324. doi: 10.1111/hiv.13014. Epub 2020 Nov 23.

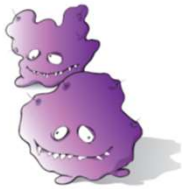
* Clinical Microbiology and Infection 28 (2022) 23–30

JOURNAL OF CLINICAL MICROBIOLOGY, May 2011, p. 1872–1878 Vol. 49, No. 5
0095-1137/11/$12.00 doi:10.1128/JCM.02390-10

myconostica

MycAssay Pneumocystis

Rapid detection of Pneumocystis DNA from lower respiratory tract samples using Real-Time PCR



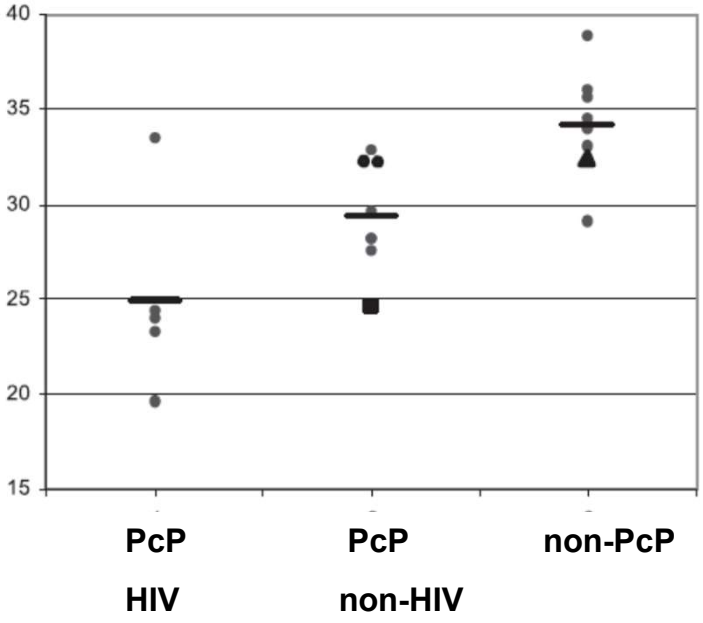
Multicenter, Prospective Clinical Evaluation of Respiratory Samples from Subjects at Risk for *Pneumocystis jirovecii* Infection by Use of a Commercial Real-Time PCR Assay▽†

Philippe M. Hauser,[1] Jacques Bille,[1] Cornelia Lass-Flörl,[2] Christian Geltner,[3] Marta Feldmesser,[4] Michael Levi,[5] Hitesh Patel,[5] Victoria Muggia,[6] Barbara Alexander,[7] Martin Hughes,[8] Sarah A. Follett,[8] Xiaohui Cui,[8]‡ Flora Leung,[8]§ Gillian Morgan,[8] Adrian Moody,[8] David S. Perlin,[9] and David W. Denning[8,10,11,12]*

TABLE 3. Comparison of Merifluor immunofluorescence test with MycAssay Pneumocystis results[a]

MycAssay Pneumocystis result	No. of patients with the indicated result			
	Clinically diagnosed with PCP (n = 14)		Clinically diagnosed with a condition other than PCP (n = 69)	
	IF$^+$	IF$^-$	IF$^+$	IF$^-$
Positive	12	1	0	7
Negative	1	0	0	62

[a] A total of 83 patients were tested.



Detection of *Pneumocystis jirovecii* by Quantitative PCR To Differentiate Colonization and Pneumonia in Immunocompromised HIV-Positive and HIV-Negative Patients

In-house-PCR

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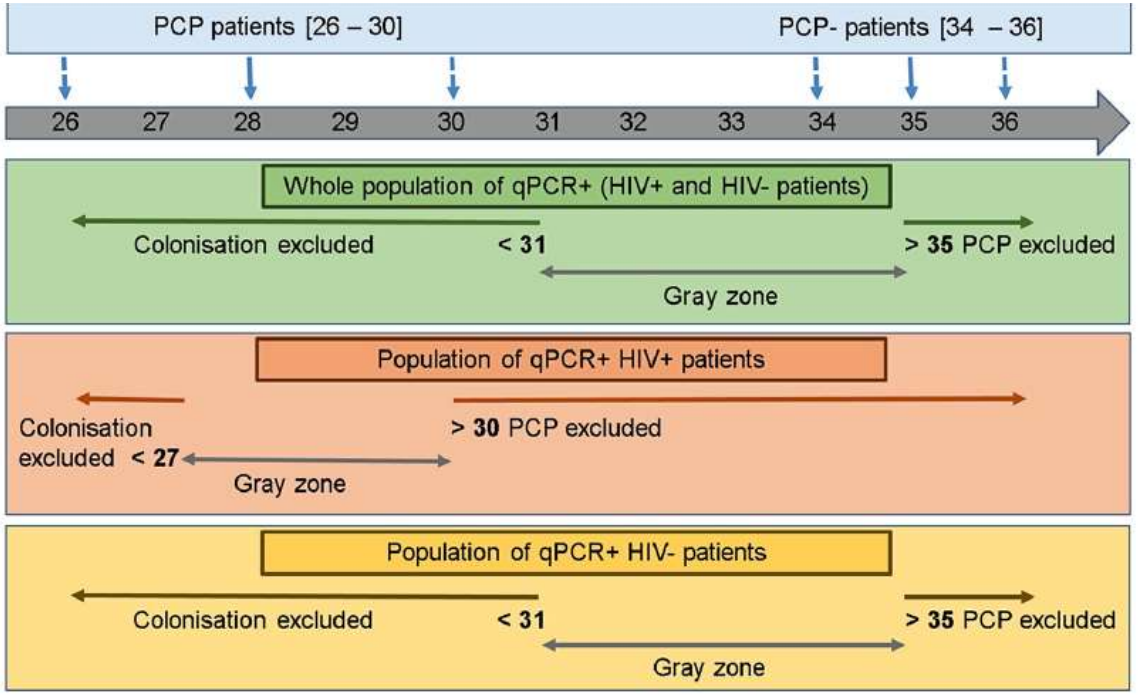
TABLE 3 C_T values for exclusion of a diagnosis and the corresponding values of sensitivity and specificity according to the population studied

	Exclusion of PCP			Exclusion of colonization		
Patient group	C_T value	Sensitivity	Specificity	C_T value	Sensitivity	Specificity
Whole qPCR$^+$ population	>35	0.80	0.63	<31	0.66	0.80
HIV$^+$ patients	>30	0.80	0.79	<27	0.73	1.00
HIV$^-$ patients	>35	0.80	0.60	<31	0.59	0.80

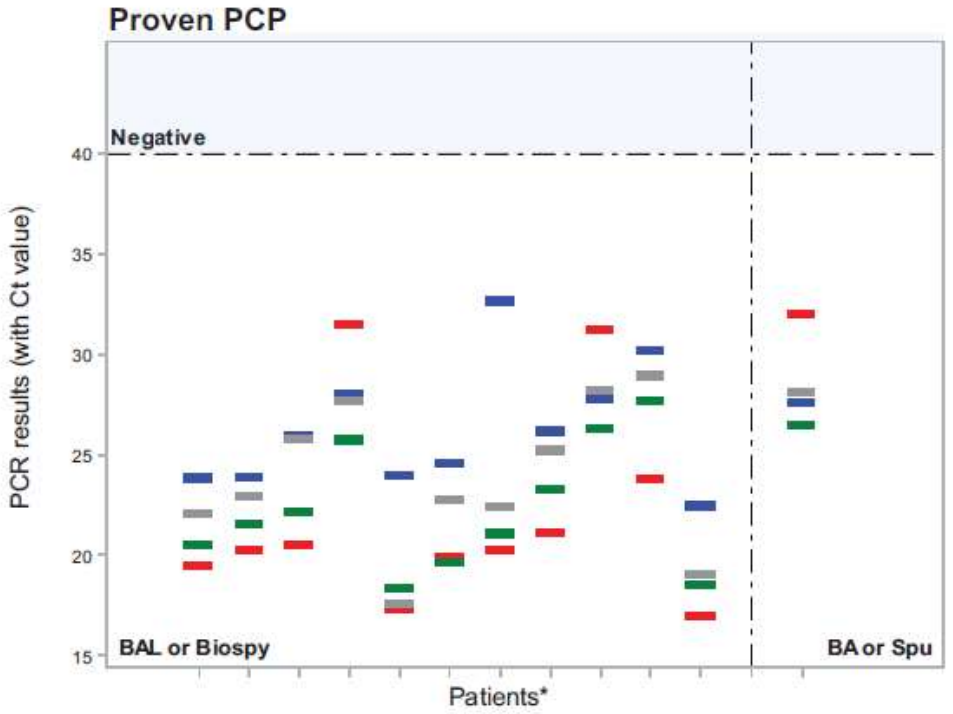


Performances of Four Real-Time PCR Assays for Diagnosis of *Pneumocystis jirovecii* Pneumonia

Milène Sasso,[a] Elsa Chastang-Dumas,[a] Sophie Bastide,[b] Sandrine Alonso,[b] Catherine Lechiche,[c] Nathalie Bourgeois,[d] Laurence Lachaud[a]

148 Proben, AmpliSens, MycAssay (Myconostica), Bio-Evolution

Übereinstimmung 82 - 97 %



Evaluation of a commercial Loop-mediated Isothermal Amplification (LAMP) assay for rapid detection of *Pneumocystis jirovecii*

Ulrike Scharmann[1] | Lisa Kirchhoff[1] | Dirk Schmidt[1] | Jan Buer[1] | Joerg Steinmann[1,2] | Peter-Michael Rath[1]

TABLE 1 Description of patient cohort included in this study (n = 146)

Gender [n (%)]	
Male	89 (61)
Female	57 (39)
Age [years]	
Median	59
Min.	18
Max.	86
Underlying condition [n (%)]	
HIV	11 (8)
Non-HIV	135 (92)
Heart surgery	25 (17)
Haematological malignancy	22 (15)
Lung disease	21 (13)
Autoimmune disease	18 (12)
Solid organ transplantation	17 (12)
Solid tumour	12 (8)
Other immunodeficiency	20 (12)

Abbreviations: %, per cent; Max., maximum; Min., minimum; n, number of patients.

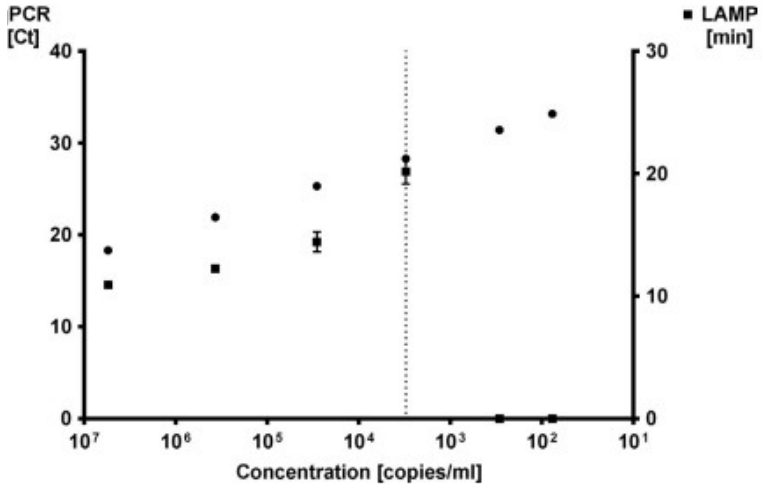


TABLE 5 Data analysis of LAMP assay. Statistical analysis was based on a positive signal in qPCR and LAMP

Statistical data	
Positive predictive value (%)	96
Negative predictive value (%)	96
Sensitivity (%)	84
Specificity (%)	99
Analytic sensitivity (copies/mL)	~4 x 10^3

Abbreviations: %, per cent; mL, millilitre.

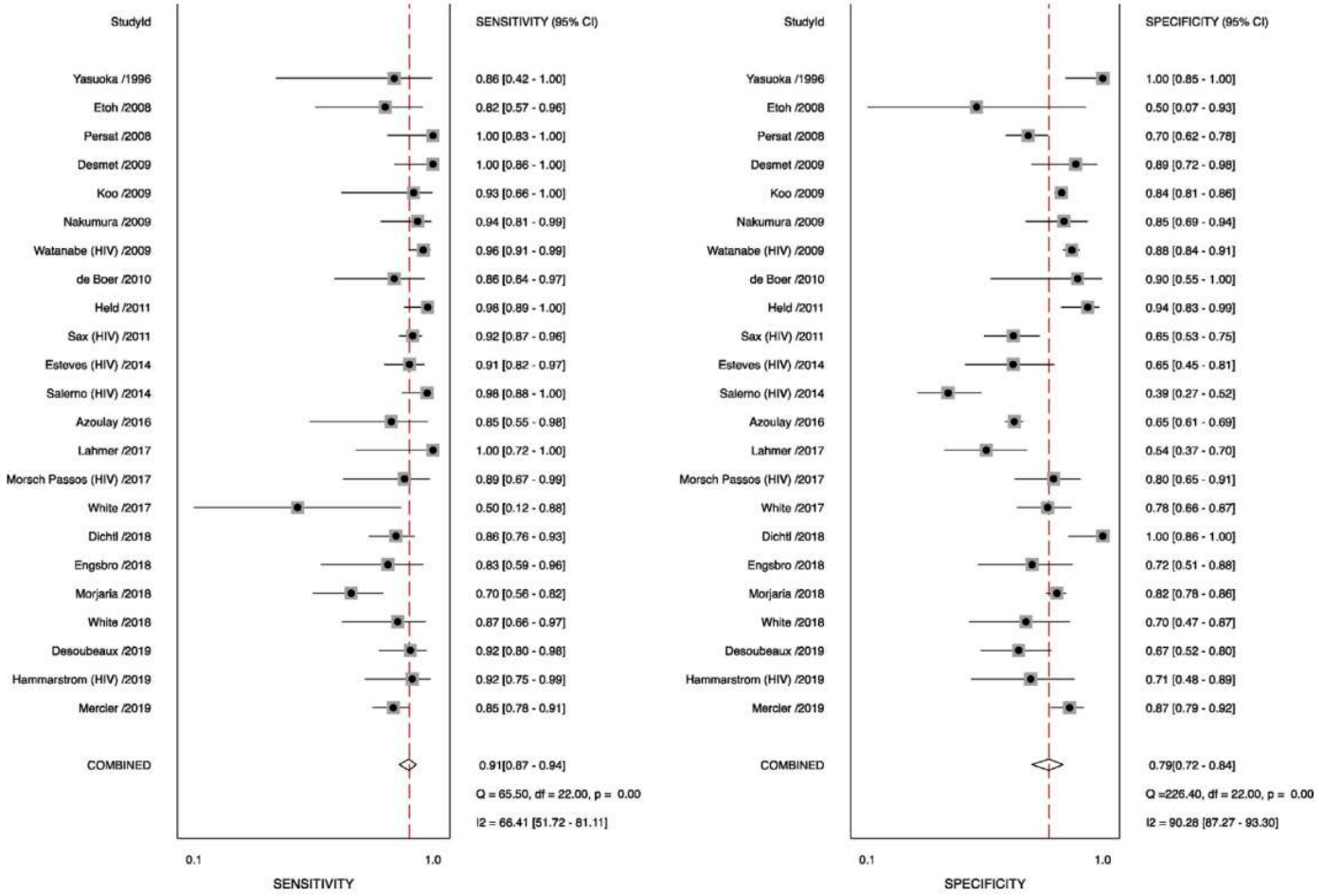
3/162 Proben mikroskopisch positiv, qPCR: Ct 17-19, LAMP: 10-13 Minuten

Realstar *P. jirovecii* 1.0 altona-Diagnostics GmbH, Hamburg / easyplex P. jirovecii LAMP, Amplexdiagnostics GmbH

Mycoses. 2020;63:1107–1114.

Diagnostic accuracy of serum (1-3)-β-D-glucan for *Pneumocystis jirovecii* pneumonia: a systematic review and meta-analysis

Olivier Del Corpo [1], Guillaume Butler-Laporte [2], Donald C. Sheppard [2, 3, 4], Matthew P. Cheng [2, 3], Emily G. McDonald [3, 5, 6], Todd C. Lee [2, 3, 5, 6, *]



HIV

Sensitivität 94 %

Spezifität 83 %

Non-HIV

Sensitivität 86%

Spezifität 83 %

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Pneumocystis jirovecii

- **Biologisch ein Pilz** — **ohne Ergosterol**
- **Bei Säugetieren weit verbreitet**
- **Maximal an Wirt adaptiert** — **lange Co-Evolution, (nicht) anzüchtbar, kein Tiermodell für *P. jirovecii***
- **Habitat / Übertragungsweg** — **Alveolen / Luft (Zysten ! Ausbrüche beschrieben)**
- **Erstkontakt in früher Jugend** — **Seroprävalenz 80 % bis zum 5. Lebensjahr**
- **Prävalenz bei Gesunden** — **hoch (> 60%)**
- **Zunehmende Häufigkeit von Erkrankungen bei nicht-HIV-Patient*innen**
  (atypische Radiologie, schweres klinisches Bild bei geringerem Keimload)
- **Proinflammatorischer Effekt der Kolonisation bei chronischen pulmonalen Erkrankungen ?**
- **Diagnostik: quantitative PCR (Abgrenzung klinische relevante von klinisch irrelevanter Kolonisation schwierig)**
  LAMP (weniger sensitiv als qPCR)
  ß-D-Glukan hohe diagnostische Sensitivität bes. bei AIDS. Als Verlaufskontrolle bedingt geeignet.

Clinical Microbiology Reviews

Pneumocystis jirovecii pneumonia in people living with HIV: a review

Emily G. McDonald,[1,2,3] Avideh Afshar,[4] Bander Assiri,[2]

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