Research on *Mycobacterium avium* during the period 1995 to 2009

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ABSTRACT: Papers on *Mycobacterium avium*, published between 1995 and 2009 that are indexed in the databases Web of Science® (Thomson Reuters) and PubMed (U.S. National Library of Medicine) were analysed and 3377 papers, published by 11 197 authors from 2630 institution and 75 countries were compared. *Mycobacterium avium* is represented by four subspecies (*M. avium* subsp. *avium*, *M. avium* subsp. *silvaticum*, *M. avium* subsp. *hominissuis*, and *M. avium* subsp. *paratuberculosis*). Mycobacteria play an important role as human and animal pathogens and represent a potential risk to consumers as food and environmental pathogens and immunomodulators.

Keywords: publications; analysis; health risk; food safety

The importance of mycobacteria and their impact on human health has been widely acknowledged in the literature, and the number of publications dedicated to this problem is steadily increasing. Mycobacterial species not belonging to the *Mycobacterium tuberculosis* complex are known as environmental or potentially pathogenic mycobacteria. Of these, the *Mycobacterium avium* complex has been studied the most. The taxonomy of *Mycobacterium avium*, originally established on the basis of serological characteristics and virulence, has changed under the influence of more sophisticated identification methods. At present, the terminology is not clear and not used uniformly. The term '*Mycobacterium avium* complex' was originally used to define a group of closely related organisms that can be divided into two separate species, *Mycobacterium avium* and *M. intracellulare*, consisting of 28 serovars. With the development of molecular biology, the species *M. avium* has been described in more detail. *Mycobacterium avium* is comprised of four subspecies, which are known animal pathogens; however they differ in their phenotypic characteristics and host susceptibility. *Mycobacterium avium* subsp. *avium* (MAA) is primarily a bird pathogen, causing tuberculous lesions in many different organs and most commonly systemic disease. It affects mainly domestic fowl, although it has been described in a wide variety of domestic and wild bird species (Thorel et al., 1997). *Mycobacterium avium* subsp. *silvaticum* has been described as a causative agent of tuberculosis in wood pigeons (Thorel et al., 1990). It differs from MAA in its dependence on mycobactin for primary culture. *Mycobacterium avium* subsp. *hominissuis* causes mycobacteriosis in pigs and other animals, as well as humans (Mijs et al., 2002). *Mycobacterium avium* subsp. *paratuberculosis* (MAP) is the etiological agent of paratuberculosis, a chronic enteric disease in cattle and wild ruminants. Of all the *M. avium* subspecies, MAP has the greatest importance, causing economic losses (Kennedy and Benedictus, 2001; Hasonova and Pavlik, 2006; Groenendaal and Wolf, 2008; Kudahl et al., 2008; Pillars et al., 2009). Its connection to Crohn's disease has been debated for the last two decades (Bull

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et al., 2003; Scanu et al., 2007). Papers dealing with MAP or paratuberculosis have been excluded from the search results, because an analytical review paper on paratuberculosis has been published only recently (Kaevska and Hruska, 2010).

One of the main aspects of research on *Mycobacterium avium* species is their clinical relevance. There is evidence to indicate that the incidence of human disease has been steadily increasing (Griffith et al., 2007). This is probably due to the influence of many factors; for example, an increase in the frequency of diseases suppressing the immune system which in turn increases susceptibility to mycobacterial infection. An increasingly aging population in developed countries, as well as an increased presence of mycobacteria in the human environment or the development of resistance to the most commonly used desinfectants, can all play a role. *M. avium* is often described as the causal agent of pulmonary infections in eld-

Table 1. Selected books and e-articles (download the full paper PDF from http://vetmed.vri.cz to use the hyperlinks)

BOOKS

The Ecology of Mycobacteria: Impact on Animal's and Human's Health (Kazda et al., 2009)

http://www.springer.com/public+health/book/978-1-4020-9412-5
http://centaur.vri.cz/news/prilohy/pril1219.pdf
http://www.amazon.com/Ecology-Mycobacteria-Impact-Animals-Humans/dp/1402094124/ref=sr_1_39?s=STORE&ie=UTF8&qid=1285834438&sr=1-39

Molecular Mycobacteriology: Techniques and Clinical Applications

http://www.amazon.com/Molecular-Mycobacteriology-Techniques-Clinical-Applications/dp/0824702409/ref=sr_1_20?s=STORE&ie=UTF8&qid=1285833809&sr=1-20

Improved Mycobacterium avium Complex Detection Methods (AwwaRF Report)

http://www.amazon.com/Improved-Mycobacterium-Complex-Detection-Methods/dp/1843396270/ref=sr_1_3?s=books&ie=UTF8&qid=1285833426&sr=1-3

Pathogenic Mycobacteria in Water: A Guide to Public Health Consequences, Monitoring and Management

http://www.amazon.com/Pathogenic-Mycobacteria-Water-Consequences-Monitoring/dp/9241562595/ref=sr_1_32?s=STORE&ie=UTF8&qid=1285834313&sr=1-32

Tuberculosis and Nontuberculosis Mycobacterial Infections

http://www.amazon.com/Tuberculosis-Nontuberculosis-Mycobacterial-Infections-Schlossberg/dp/0071439137/ref=sr_1_33?s=STORE&ie=UTF8&qid=1285834438&sr=1-33

Mycobacterium avium Complex

http://www.amazon.com/Mycobacterium-Avium-Complex-Frederic-Miller/dp/6131697841/ref=sr_1_9?s=books&ie=UTF8&qid=1285833426&sr=1-9

Nontuberculous Mycobacteria: Nontuberculous Mycobacteria, Mycobacterium Avium Complex, Mycobacterium Kansasii, Mycobacterium Cosmeticum

http://www.amazon.com/Nontuberculous-Mycobacteria-Mycobacterium-Kansasii-Cosmeticum/dp/1155677714/ref=sr_1_18?s=STORE&ie=UTF8&qid=1285833809&sr=1-18

E-ARTICLES

M. avium – intracellulare (2010-01-12)

http://emedicine.medscape.com/article/222664-overview

M. avium complex

http://www.wrongdiagnosis.com/m/mycobacterium_avium_complex/intro.htm

Sources of Infection: Mycobacterium Avium Infections in Pigs, Humans and Birds in Norway (Science Daily 2010-02-14)

http://www.sciencedaily.com/releases/2010/02/100203091600.htm

You Can Prevent MAC (Disseminated Mycobacterium Avium Complex Disease)

http://www.cdc.gov/hiv/resources/brochures/mac.htm

Table 2. Selected review articles

Amoeba symbiosis	Schmitz-Esser et al., 2010
Mycobacterial glycopeptidolipids in pathogenesis	Schorey and Sweet, 2008
Genetic background of virulence	Jang et al., 2008
Contamination of mammalian cell culture	Lelong-Rebel et al., 2009
Atypical mycobacteriosis, diagnosis and treatment	Skoric et al., 2007 Griffith, 2007 Griffith et al., 2007 Kasperbauer and Daley, 2008 Sexton and Harrison, 2008 Fuschillo et al., 2008 Esteban and Ortiz-Perez, 2009
HIV and immunodeficiency	Wachtman and Mansfield, 2008 Bonham et al., 2008 Corti and Palmero, 2008 Herzmann and Lange, 2010 Pietras et al., 2010
Mycobacteriosis in transplant recipients	Daley, 2009
Complications of infliximab therapy	Salvana et al., 2007

erly or immunosuppressed patients (Falkinham, 1996). Environmental sources, namely potable water, showers or swimming pools are the main sources of infection, as human to human transmission has not been recorded (Falkinham, 1996; Primm et al., 2004; van Ingen et al., 2009). A recently published book has summarised the impact of mycobacteria in the environment on human and animal health (Kazda et al., 2009). Their ubiquitous nature and unique physiological characteristics enable them to survive and persist in natural as well as manmade environments thus providing a constant source of contact with humans and animals. Many publications dealing with different aspects of *Mycobacterium avium* complex interaction with humans or animals have been published (Table 1 and Table 2).

The Web of Knowledge® portal (Thomson Reuters) is a unique tool that can be used to analyse literature from a very representative pool of scientific journals. Previous analyses of publications pertaining to paratuberculosis (Hruska, 2004; Kaevska and Hruska, 2010) have demonstrated its usefulness. The aim of this analysis is concerned with the number of publications on *Mycobacterium avium* (excluding paratuberculosis) and to assess the trend in research for the past 15 years, during which time the number of papers on MAP and paratuberculosis has evidently increased.

MATERIAL AND METHODS

Web of Science, Science Citations Index Expanded, Social Sciences Citation Index and Art and Humanities Index databases® (Thomson Reuters) were used to search for articles published between 1995 and 2009 and separately, 1995 to 1999, 2000 to 2004 and 2005 to 2009 using the search profile [("*Mycobacterium avium*" OR "M. avium" NOT (paratuberculosis OR Johne's OR Johnes")]. Search results were refined using the following key words: water, soil, (manure OR faeces OR feces OR slurry), milk, meat and environment.

Table 3. Search results using the profile ("Mycobacterium avium" OR "M. avium") NOT (paratuberculosis OR Johne's OR Johnes)

	1995–1999	2000–2004	2005–2009	1995–2009
Web of Science				
All publications	1497	1003	877	3377
Authors	5173	3757	3779	11 197
Institutions	1263	1101	1129	2630
Countries	59	60	53	75
Water	46	71	89	206
Soil	11	14	18	43
Manure OR faeces OR feces OR slurry	6	2	6	14
Milk	3	0	0	3
Meat	2	2	5	9
Environment	33	35	44	112
PubMed				
All publications	1784	1173	1012	3965
Limit				
Human	1415	856	754	3022
Animal	342	284	220	845
Water	36	58	71	165
Soil	13	14	13	40
Manure OR faeces OR feces OR slurry	20	6	7	33
Milk	4	2	2	8
Meat	7	5	6	18
Environment	58	56	63	177

The Web of Science database has unique tools that enable different analyses to be performed on the search results. These were used to analyse the authors, institutions, countries and funding agencies which have the highest number of research papers in this field over the last five years. The following parameters were applied and the results are presented:

- Summary of the number of papers published, using "*Mycobacterium avium*" and related keywords as the topic in PubMed and WOS databases.
- Authors who published ten or more papers on the topic in the last five years, compared to their publication activity in the two previous five year periods.
- Institutions that published ten or more papers on the topic in the last five years, compared to their publication activity in the two previous five year periods.
- Countries that published twenty or more papers on the topic in the last five years, compared to their publication activity in the two previous five year periods.
- The top 20 most frequently cited papers on the topic in the last 15 years.

The database PubMed© (U.S. National Library of Medicine) was searched for papers, published in the same time span using the same search profiles and limits. The searches from PubMed were also limited to humans and to animals.

Table 4. Authors publishing ten or more papers in the period from 2005 to 2009, in comparison to their publication activity in the previous five year periods

	Authors	2005–2009	2000–2004	1995–1999
1	Koh WJ	25	2	
2	Kwon OJ	23	2	
3	Yano I	18	3	3
4–5	Appelberg R	16	20	18
4–5	Bermudez LE	16	31	37
6	Pavlik I	14	8	2
7	Lee KS	13	2	1
8	Naka T	11	1	
9	Matlova L	10	4	

RESULTS AND DISCUSSION

A summary of the number of papers published using the search profile [("Mycobacterium avium" OR "M. avium") NOT (paratuberculosis OR Johne's OR Johnes)] in PubMed and WOS databases is presented in Table 3. The total number of publications has decreased during the five years periods investigated (from 1995 to 2009). There are differences in the absolute numbers between the databases due to their differing journal coverage, but the general trends are evident in both databases.

Tables 4 to 7 display the search result analyses performed using the Web of Science utilities. Table 4 presents authors that published ten or more papers in the last five years. It reveals that all the authors were active in the field for at least ten years,

Table 5. Institutions with 10 or more publications in the field between 2005 and 2009, in comparison to their publication activity in the previous five-year periods

	Institutions		2005–2009	2000–2004	1995–1999
1	Sungkyunkwan University	▲	24	2	
2	Harvard University		18	49	41
3	Oregon State University	▲	16	10	
4	University of Porto		15	21	26
5–6	National Institute for Allergy and Infectious Diseases		14	24	30
5–6	Veterinary Research Institute, Brno	▲	14	8	2
7	Duke University		13	12	16
8	University of Notre Dame	▲	11	9	
9–11	Boston University		10	17	24
9–11	Johns Hopkins University		10	21	34
9–11	University of Texas		10	25	66

▲ = increase, compared to 2000 to 2004

Table 6. Countries with 20 or more publications during 2005–2009, in comparison to the previous five-year periods

	Country		2005–2009	2000–2004	1995–1999
1	USA	▼	344	499	834
2	Japan		92	94	69
3	Germany	▼	50	62	73
4	France	▼	49	56	138
5	Spain		42	39	37
6	England	▼	39	67	95
7	South Korea	▲	36	6	5
8	Italy	▼	32	46	61
9–10	Canada		31	29	50
9–10	India	▲	31	14	6
11–12	Brazil	▲	27	23	11
11–12	Portugal		27	27	27
13	Czech Republic	▲	25	22	10
14–15	Australia	▼	21	43	42
14–15	Netherlands	▲	21	12	17

▼ = greater than 10% decrease, compared to 2000 to 2004
▲ = increase, compared to 2000 to 2004

five of them for 15 years. It is evident that institutions producing ten or more papers published between 2005 and 2009, must have all been working on MAA for at least ten years, with eight of them for 15 years (Table 5). The declining number of publications on the topic shown in Table 5 (with the exception of Sungkyunkwan University, Oregon State University, the Veterinary Research Institute, Brno and the University of Notre Dame) is in agreement with the general trend shown in Table 3. Interest in research on MAA is evident in 15 countries from five continents with 21 or more papers published in the last five years (Table 6). The decline in the number of papers published by authors from the USA, Germany, France, England, Italy, and Australia in 2005 to 2009 exceeds 10% when compared to the previous five year period. In contrast, authors from South Korea, India, Brazil, the Czech Republic and the Netherland published more papers in the most recent period than in the one previous to it.

Table 7 is a list of the most frequently cited papers. It is obvious that the most frequently cited paper by Palella et al. (1998) does not owe its 4425 citations to work on MAA but rather its link to HIV. However, papers dealing with the epidemiology of nontuberculous mycobacteria by Falkinham (1996), cited 414 times and by Griffith et al. (2007), cited 320 times reflect actual contributions to studies on *M. avium*.

Overall, the number of publications on *M. avium* is not increasing, contrary to those dealing with *Mycobacterium avium* subsp. *paratuberculosis* (Kaevska and Hruska, 2010). Nevertheless, the interest in MAA remains high, due to the series of opportunistic infections it can cause in immunocompromised humans. Moreover, pathological lesions in pigs caused by non-tuberculous mycobacteria can result in great economical losses and pose a risk to some consumers (Shitaye et al., 2006). Apart from the impact of MAA on human and animal health, this species is also the subject of interest for ecologists, investigating its persistence in the environment.

Table 7. Top 20 most frequently cited papers

4435	Palella FJ, Delaney KM, Moorman AC, Loveless MO, Fuhrer J, Satten GA, Aschman DJ, Holmberg SD (1998) **Declining morbidity and mortality among patients with advanced human immunodeficiency virus infection** New England Journal of Medicine 338, 853–860
641	Collins LA, Franzblau SG (1997) **Microplate Alamar blue assay versus BACTEC 460 system for high-throughput screening of compounds against Mycobacterium tuberculosis and Mycobacterium avium** Antimicrobial Agents and Chemotherapy 41, 1004–1009
527	Lien E, Sellati TJ, Yoshimura A, Flo TH, Rawadi G, Finberg RW, Carroll JD, Espevik T, Ingalls RR, Radolf JD, Golenbock DT (1999) **Toll-like receptor 2 functions as a pattern recognition receptor for diverse bacterial products** Journal of Biological Chemistry 274, 33419–33425
451	Means TK, Wang SY, Lien E, Yoshimura A, Golenbock DT, Fenton MJ (1999) **Human toll-like receptors mediate cellular activation by Mycobacterium tuberculosis** Journal of Immunology 163, 3920–3927
448	Weinstein MP, Towns ML, Quartey SM, Mirrett S, Reimer LG, Parmigiani G, Relier LB (1997) **The clinical significance of positive blood cultures in the 1990s: A prospective comprehensive evaluation of the microbiology, epidemiology, and outcome of bacteremia and fungemia in adults** Clinical Infectious Diseases 24, 584–602
441	Hogg RS, Heath KV, Yip B, Craib KJP, O'Shaughnessy MV, Schechter MT, Montaner JSG (1998) **Improved survival among HIV-infected individuals following initiation of antiretroviral therapy** Journal of the American Medical Association 279, 450–454
414	Falkinham JO (1996) **Epidemiology of infection by nontuberculous mycobacteria** Clinical Microbiology Reviews 9, 177–215
322	Orenstein JM, Fox C, Wahl SM (1997) **Macrophages as a source of HIV during opportunistic infections** Science 276, 1857–1861
320	Griffith DE, Aksamit T, Brown-Elliott BA, Catanzaro A, Daley C, Gordin F, Holland SM, Horsburgh R, Huitt G, Iademarco MF, Iseman M, Olivier K, Ruoss S, von Reyn CF, Wallace RJ, Winthrop K (2007) **An official ATS/IDSA statement: Diagnosis, treatment, and prevention of nontuberculous mycobacterial diseases** American Journal of Respiratory and Critical Care Medicine 175, 367–416
314	Boons GJ (1996) **Strategies in oligosaccharide synthesis** Tetrahedron 52, 1095–1121

Table 7 contiued

267	Race EM, Adelson-Mitty J, Kriegel GR, Barlam TF, Reimann KA, Letvin NL, Japour AJ (1998) **Focal mycobacterial lymphadenitis following initiation of protease-inhibitor therapy in patients with advanced HIV-1 disease** Lancet 351, 252–255
259	Mocroft A, Katlama C, Johnson AM, Pradier C, Antunes F, Mulcahy F, Chiesi A, Phillips AN, Kirk O, Lundgren JD (2000) **AIDS across Europe, 1994–98: the EuroSIDA study** Lancet 356, 291–296
256	Nicholson S, Bonecinialmeida MDG, Silva JRLE, Nathan C, Xie QW, Mumford R, Weidner JR, Calaycay J, Geng J, Boechat N, Linhares C, Rom W, Ho JL (1996) **Inducible nitric oxide synthase in pulmonary alveolar macrophages from patients with tuberculosis** Journal of Experimental Medicine 183, 2293–2302
216	Fidock DA, Wellems TE (1997) **Transformation with human dihydrofolate reductase renders malaria parasites insensitive to WR99210 but does not affect the intrinsic activity of proguanil** Proceedings of the National Academy of Sciences of the United States of America 94, 10931–10936
216	French MA, Price P, Stone SF (2004) **Immune restoration disease after antiretroviral therapy** Aids 18, 1615–1627
214	Freedberg KA, Losina E, Weinstein MC, Paltiel AD, Cohen CJ, Seage GR, Craven DE, Zhang H, Kimmel AD, Goldie SJ (2001) **The cost effectiveness of combination antiretroviral therapy for HIV disease** New England Journal of Medicine 344, 824–831
210	Barry M, Gibbons S, Back D, Mulcahy F (1997) **Protease inhibitors in patients with HIV disease – Clinically important pharmacokinetic considerations** Clinical Pharmacokinetics 32, 194–209
210	DeSimone JA, Pomerantz RJ, Babinchak TJ (2000) **Inflammatory reactions in HIV-1-infected persons after initiation of highly active antiretroviral therapy** Annals of Internal Medicine 133, 447–454
210	Shelburne SA, Hamill RJ, Rodriguez-Barradas MC, Greenberg SB, Atmar RL, Musher DM, Gathe JC, Visnegarwala F, Trautner BW (2002) **Immune reconstitution inflammatory syndrome – Emergence of a unique syndrome during highly active antiretroviral therapy** Medicine 81, 213–227
206	Hesse M, Modolell M, La Flamme AC, Schito M, Fuentes JM, Cheever AW, Pearce EJ, Wynn TA (2001) **Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines in vivo: Granulomatous pathology is shaped by the pattern of L-arginine metabolism** Journal of Immunology 167, 6533–6544

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