TB e NTM : divergenze parallele ?

Roberto Parrella

UOC Malattie Infettive ad indirizzo respiratorio
AORN Ospedali dei Colli
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Le elezioni del 4 marzo 2018 si sono svolte nel segno delle divergenze. Fra il vecchio e il nuovo. Il popolo e l'*establishment*. Lega e M5s sono le due forze politiche uscite vincenti. Due soggetti e due identità divergenti che però viaggiano e muovono nella stessa direzione perché 'divergono' da nemici comuni. Non solo e non più la *casta* ma l'*establishment* politico, istituzionale, economico, finanziario. A loro basta distinguersi, distanziarsi, anzi: dissociarsi da tutti gli altri. Per questo è sufficiente un contratto che non delinei un sistema di valori, ma solo un accordo su temi e obiettivi specifici sui quali convergere, anzi divergere rispetto a 'tutti gli altri'. Entrambi coesi nello sfidare la democrazia rappresentativa in nome della democrazia diretta. Anzi: immediata.

DIZIONARIO

ENCICLOPEDICO

DELLE MATEMATICHE

DELLI SIGNORI

AB. BOSSUT, LA LANDE ec.

TRADUZIONE DAL FRANCESE

Arricchita di Annotazioni, ed Aggiunte

DEL TRADUTTORE ITALIANO

TOMO QUARTO.

PADOVA M. DCCC.

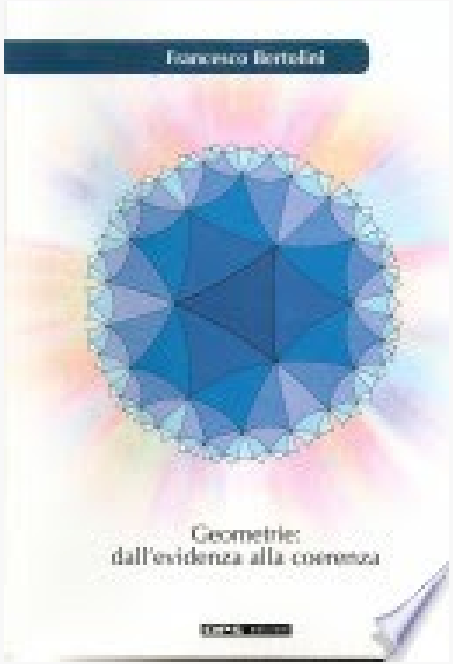
NEL SEMINARIO APPRESSO TOMMASO BETTINELLI

CON LICENZA DE' SUPERIORI.

non è più difficile a sciogliersi. Poichè la menoma cognizione dei principj della Geometria farà agevolmente vedere che acciò le linee *AB*, *cd* sieno uguali, e che acciò le linee *Ac*, *Bd* sieno linee rette parallele, conviene che le linee *AC*, *BD*, sieno due linee rette divergenti. In quanto alla quantità della loro divergenza, cioè, della quantità della quale esse divergono l'una dall'altra, questa quantità dipende dalla grandezza dell'angolo *dBD* che il piano apparente *CABd* fa con il piano reale *ABCD*, e spetta all'esperienza il far conoscere quest'angolo; intanto senza imbrogliarsi nel cercarlo, si potrebbe scoprire la posizione delle linee *AC*, *BD*, in un'altra maniera, che sarebbe di attaccare in *A* ed in *B* l'estremità di due corde lunghe e di un colore risaltante assai, e divertire queste corde l'una dall'altra, au-

aumentando, o sminuindo successivamente la loro divergenza, fino a che l'occhio collocato in *O* le giudicasse parallele.

Avendo la divergenza delle linee *AC*, *BD*, si avrebbe reciprocamente l'angolo *dBD* del piano apparente, e del piano reale, ma si può avere direttamente quest'angolo in un'altra maniera, col mezzo di due filari d'alberi paralleli; si porrà ai piedi d'uno degli alberi li più lontani, per esempio in *D*, una corda di colore risaltante assai, e si tenderà questa corda sul terreno, avvicinandolo all'occhio *O*, fino a che essa apparisca in una situazione parallela al filare *AC*; ciò che sarà facile



Un'altra situazione, in cui il comportamento delle rette può essere approssimato in forma euclidea, è data dalle rette parallele divergenti, per punti vicini alla loro perpendicolare comune.

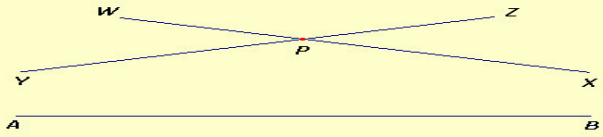
Per studiare le proprietà delle rette parallele divergenti, si rammenti che il teorema E27 prova che, se due rette formano angoli alterni interni uguali tra loro con una terza retta, allora le prime due rette risultano parallele.

Esso è un risultato che non dipende dal 5° postulato ed è quindi valido anche nella geometria iperbolica; ma, in quest'ultimo sistema, le parallele, ossia le rette che non si incontrano, si dividono in due categorie: le parallele asintotiche e le parallele divergenti.

Le parallele iperboliche

- TEOREMA 1

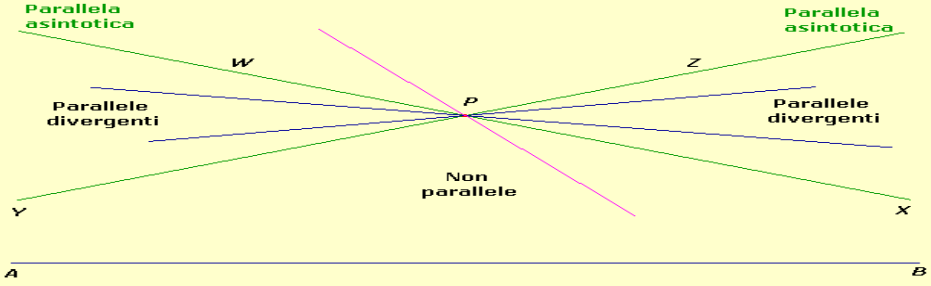
Nella situazione descritta nel POSTULATO 1*, ogni retta passante per P che entra nell'angolo ^ZPX è parallela ad AB.*



Le rette passanti per P si dividono in due categorie:
una di cui fanno parte le infinite rette che entrano nell'angolo *^YPX*, le quali, se prolungate, intersecano *AB* o il suo prolungamento;
l'altra di cui fanno parte le rette *YPZ* e *WPX* e le infinite rette che entrano nell'angolo *^ZPX*, le quali, per quanto prolungate, non incontrano mai la retta *AB* né il suo prolungamento. Queste ultime sono dunque parallele ad *AB*.
All'interno della seconda categoria *YPZ* e *WPX* occupano una posizione privilegiata, segnano infatti il confine fra una categoria e l'altra.

- DEFINIZIONE 1

Nella situazione descritta dal POSTULATO 1*, le rette YPZ e WPX si dicono parallele asintotiche per P ad AB, e le rette passanti per P che entrano in ^ZPX si dicono parallele divergenti per P ad AB.*



Basterà ricordare che le parallele asintotiche sono le due più vicine ad *AB* (nella figura sono disegnate in verde), e le parallele divergenti sono tutte le altre parallele. Proseguendo nella trattazione vedremo il significato degli aggettivi "asintotiche" e "divergenti".

NOTA
La distinzione tra parallelismo asintotico e parallelismo divergente è fatta in riferimento a punti specifici come testimonia il ricorrere della locuzione "per *P*" nella DEFINIZIONE 1. Per ora non possiamo parlare di una retta semplicemente come di una parallela asintotica o di una parallela divergente senza fare riferimento ad un punto particolare. Vedremo in seguito (TEOREMA 3 e COROLLARIO) che la proprietà di parallelismo, sia asintotico che divergente, è una proprietà della retta globalmente intesa.

Mycobacterium tuberculosis complex

Nontuberculous Mycobacteria (NTM / MOTT)

Storie parallele/divergenti ????

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Classification of mycobacterial species causing human disease

1) ***M. tuberculosis* complex**	**Slowly growing nontuberculous mycobacteria** 4)
M. tuberculosis	**Photochromogens**
M. bovis	*M. kansasii*
M. africanum	*M. marinum*
M. microti	**Scotochromogens**
M. canetti	*M. gordonae*
2) ***M. leprae***	*M. scrofulaceum*
3) **Rapidly growing nontuberculous mycobacteria**	**Nonchromogens**
M. fortuitum complex	*M. avium* complex
M. fortuitum	*M. avium*
M. peregrinum	*M. intracellulare*
M. porcinum	*M. terrae* complex
M. chelonae	*M. ulcerans*
M. abscessus	*M. xenopi*
M. abscessus	*M. simiae*
M. bolletii (previously *M. massiliense*)	*M. malmoense*
M. smegmatis	*M. szulgai*
M. mucogenicum	*M. asiaticum*
	M. haemophilum

The species have been divided into three groups: rapidly growing NTM, slowly growing NTM, and members of the *Mycobacterium tuberculosis* complex.

MICOBATTERI

***Mycobacterium tuberculosis* complex**

TUTTI PATOGENI

NTM (circa 200)

SOLO ALCUNI PATOGENI

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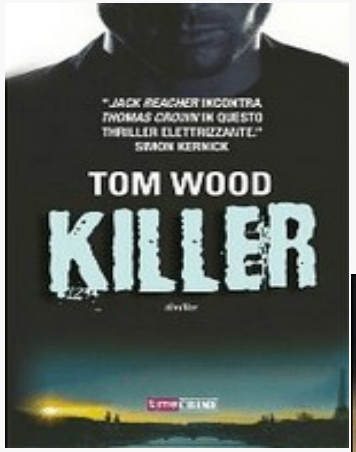
Ecology of Nontuberculous Mycobacteria—Where Do Human Infections Come from?

Joseph O. Falkinham, III, PhD[1]

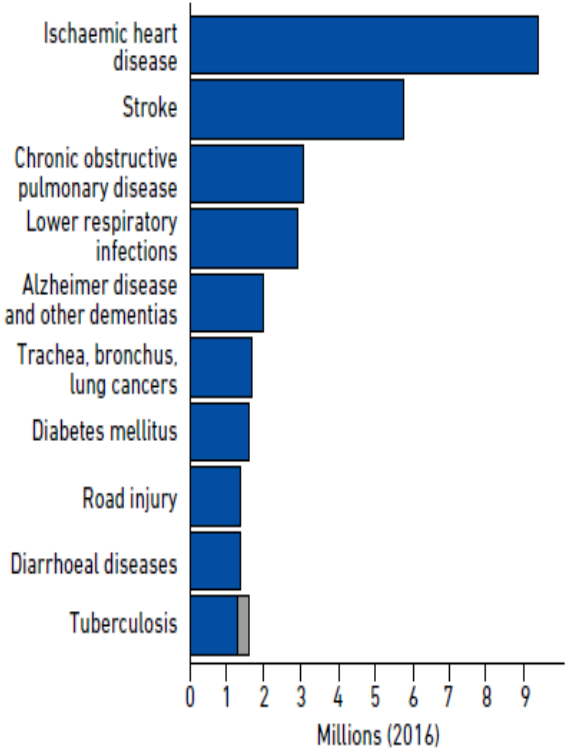
Table 1 Major pathogenic nontuberculous mycobacteria

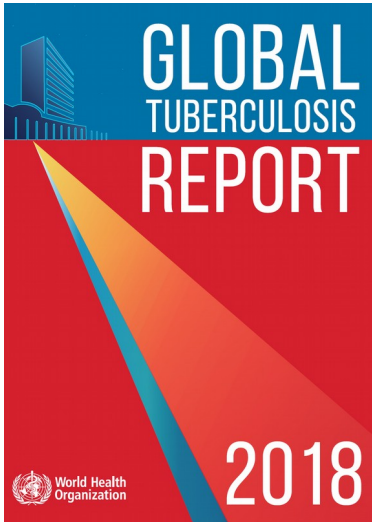
Species	Distinguishing features
Slowly growing *Mycobacterium* spp.	
Mycobacterium avium	
Mycobacterium intracellulare	
Mycobacterium kansasii	
Mycobacterium marinum	Infections associated with fish or aquaculture
Mycobacterium malmoense	
Mycobacterium xenopi	Temperature tolerant, hotwater–associated infections
Rapidly growing *Mycobacterium* spp.	
Mycobacterium fortuitum	
Mycobacterium abscessus	Infections in cystic fibrosis patients
Mycobacterium chelonae	

PATOGENO «PROFESSIONISTA» Vs «ASPIRANTI PATOGENI» (Opportunisti occasionali)

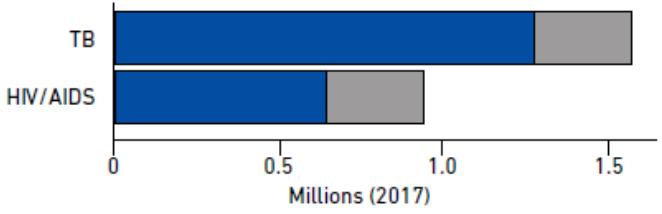


Top causes of death worldwide in 2016.[a,b]
Deaths from TB among HIV-positive people are shown in grey.



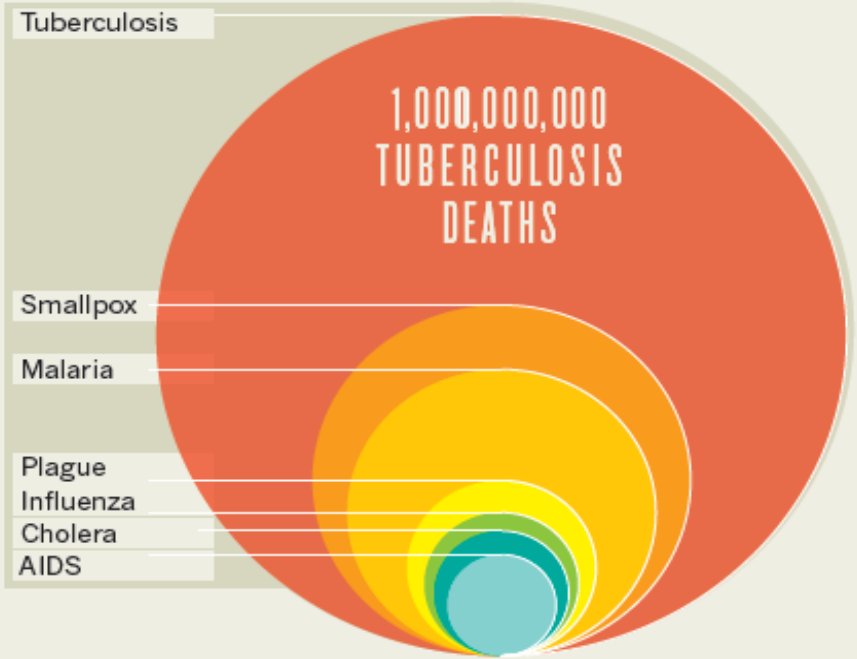


Estimated number of deaths from HIV/AIDS and TB in 2017. Deaths from TB among HIV-positive people are shown in grey.[a,b]



THE BIGGEST KILLER

Tuberculosis has killed more than any other infectious disease in history. Over a billion lives in the past two hundred years.



A MORTAL FOE

The Big Killer

NATURE | VOL 502 | 10 OCTOBER 2013

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EPIDEMIOLOGIA

CRITICITA’

	TB	NTM
DENUNCIA	OBBLIGATORIA	IN ITALIA OBBLIGATORIA; NON OBBLIGATORIA IN TUTTI I PAESI
EPIDEMIOLOGIA	STIME UFFICIALI	IGNOTA
INCIDENZA	STABILE/DIMINUZIONE	IN AUMENTO ?

Methodologic challenges that affect the study of NTM

1) In most countries NTM Pulmonary Disease is not a reportable condition

2) Isolation from an uncontaminated clinical specimen is insufficient to document disease (underlying lung disease may be colonized with NTM; clinical information + microbiological data)

3) The diagnosis comprises 3 components to include microbiological, radiographic and clinical criteria

Epidemiology of Human Pulmonary Infection with Non-Tuberculous Mycobacteria: A Review

D. Rebecca Prevots[1] and **Theodore K Marras**[2,3]

Clin Chest Med. 2015

- Population-based data from North America, Europe, and Australia, show that NTM PD prevalence continues to increase, and that prevalence is lower in Europe than in North America and Australia.
- Large tertiary-care facility based studies in East Asia (Japan, South Korea, Taiwan) also suggest high and increasing prevalence of NTM PD.
- In selected African countries, NTM were identified in 4.2% to 15% of suspected TB cases and 18–20% of persons with "chronic" suspected MDR TB.
- Improved surveillance for NTM is needed, including population based surveillance and sentinel studies

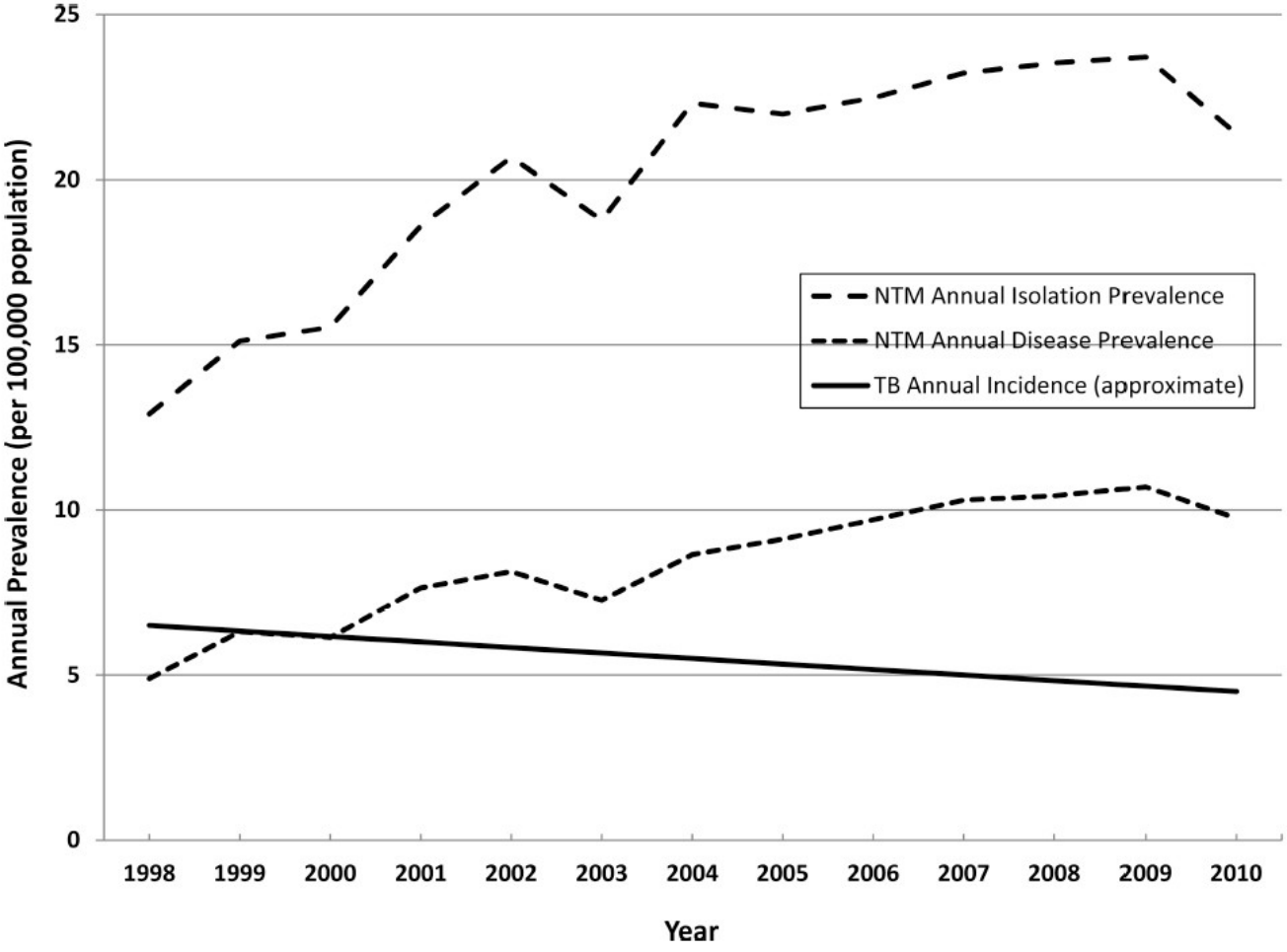

Figure 2.
Prevalence of NTM isolation and disease, and TB incidence, Canada, 1998–2010

Epidemiology of Human Pulmonary Infection with Non-Tuberculous Mycobacteria: A Review

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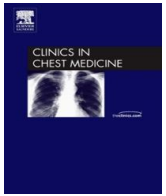
Epidemiology of Human Pulmonary Infection with Nontuberculous Mycobacteria

A Review

D. Rebecca Prevots, PhD, MPH[a,*], Theodore K. Marras, MD, MSc[b]

Clin Chest Med 36 (2015) 13–34



Annual prevalence of approx. 47/100.000 in 2007

Geografic Heterogeneity:

Hawaii	396/100.000
California	191/100.000
West	149/100.000
Southeast	131/100.000

A nationwide US study of Medicare beneficiares (≥ 65 years of age)

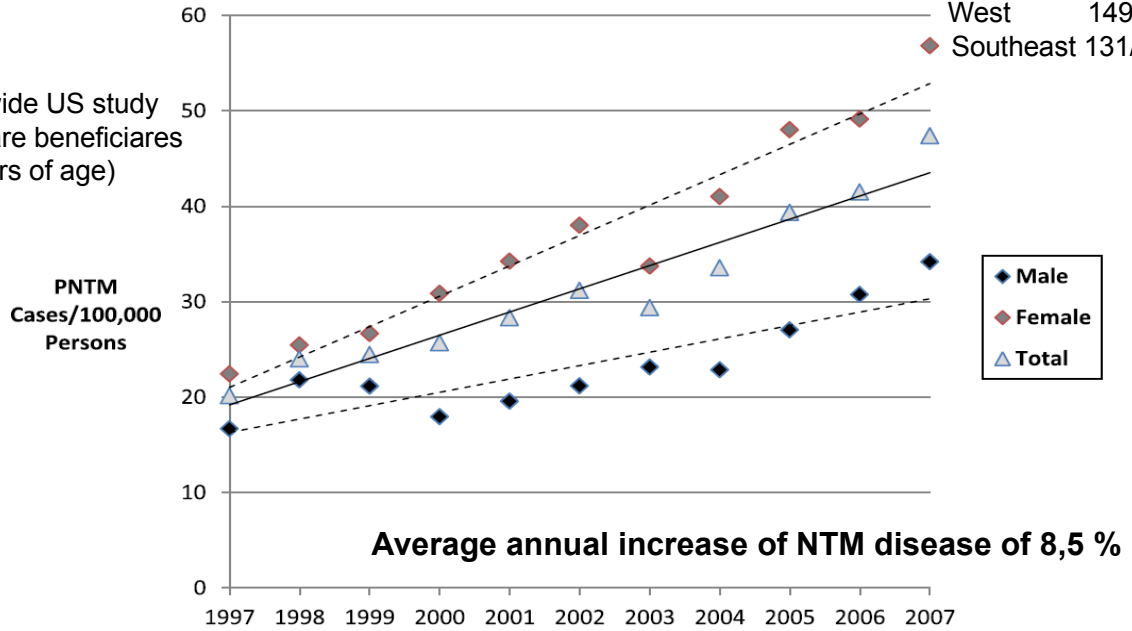


Fig. 1. Annual prevalence of pulmonary nontuberculous mycobacterial infection (PNTM) cases among a sample of US Medicare Part B enrollees by sex, 1997 to 2007.

A GROWING PROBLEM

- A nontuberculous mycobacterial (NTM) lung infection is a chronic and **debilitating lung condition** that can be easily overlooked[1-3]

- There are an estimated **86,000 cases** of NTM lung infections in the US, and that number continues to grow more than 8% every year[4,5]

Prevalence of Nontuberculous Mycobacterial Pulmonary Disease, Germany, 2009–2014

Felix C. Ringshausen, Dirk Wagner, Andrés de Roux, Roland Diel, David Hohmann, Lennart Hickstein, Tobias Welte, Jessica Rademacher

Emerging Infectious Diseases • www.cdc.gov/eid • Vol. 22, No. 6, June 2016

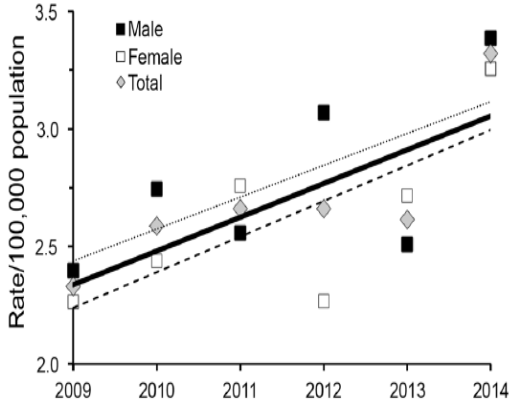


Figure 1. Trends in annual prevalence of nontuberculous mycobacterial pulmonary disease by sex and year, Germany, 2009–2014. Solid trend line indicates overall prevalence; dotted linear trend line, male prevelance; dashed linear trend line, female prevalence.

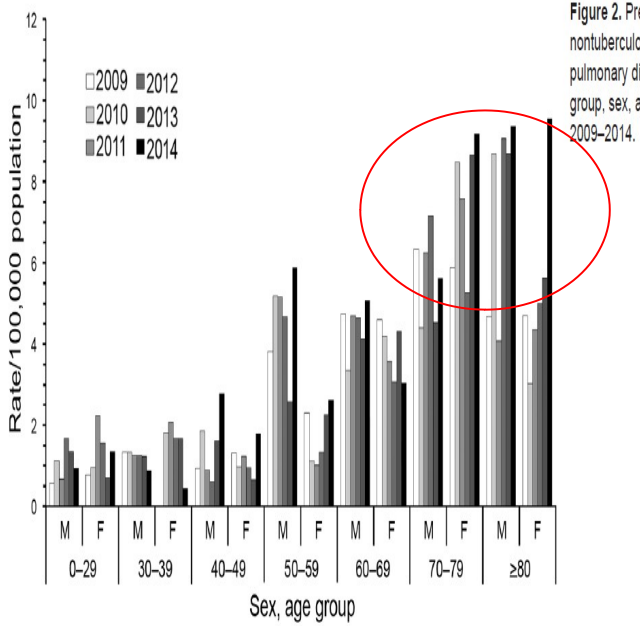
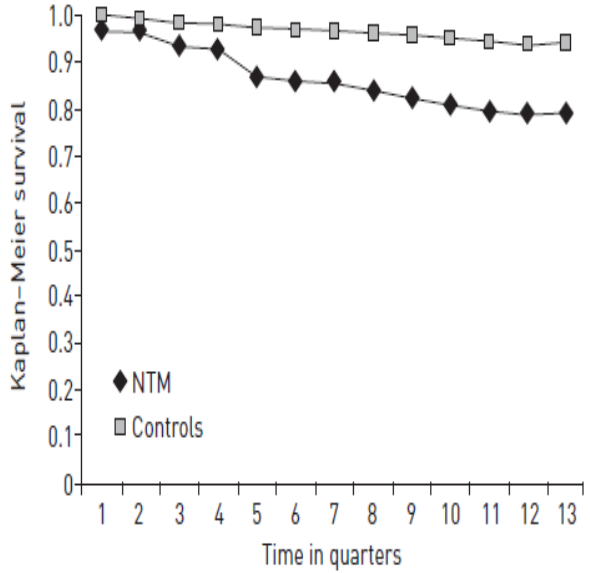


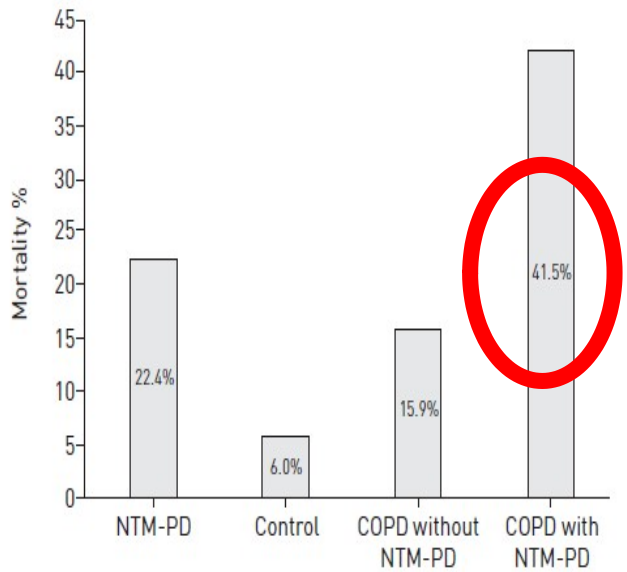
Figure 2. Prevalence rates of nontuberculous mycobacterial pulmonary disease, by age group, sex, and year, Germany, 2009–2014.

Burden of non-tuberculous mycobacterial pulmonary disease in Germany

Roland Diel[1,2], Josephine Jacob[3,4], Niklas Lampenius[5], Michael Loebinger[6], Albert Nienhaus[7,8], Klaus F. Rabe[2] and Felix C. Ringshausen[9]

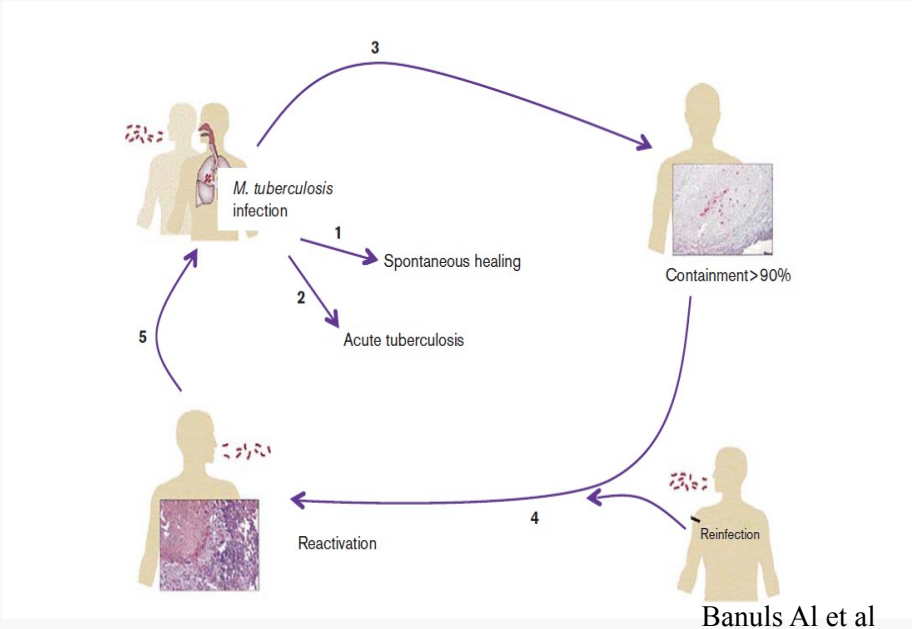
Eur Respir J 2017; 49: 1602109





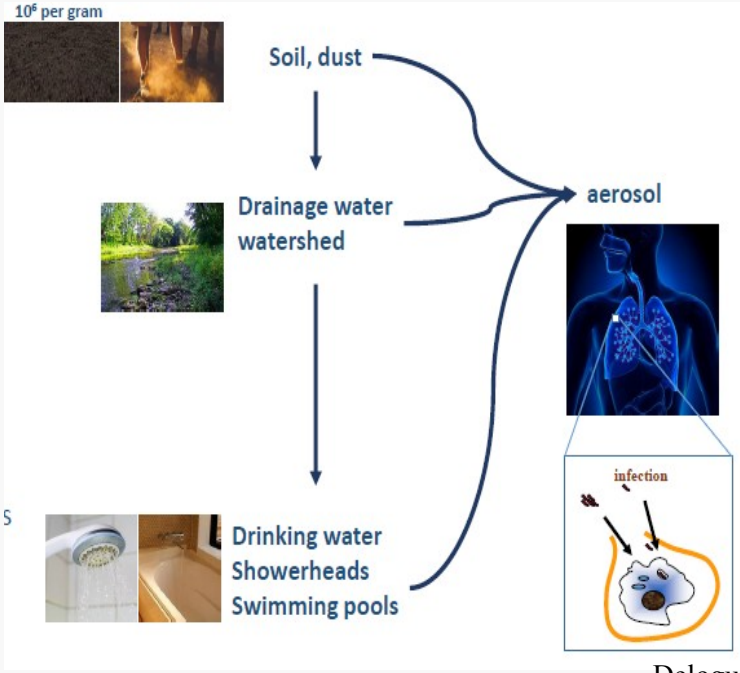
MICOBATTERI

Mycobacterium tuberculosis complex



Banuls Al et al

NTM



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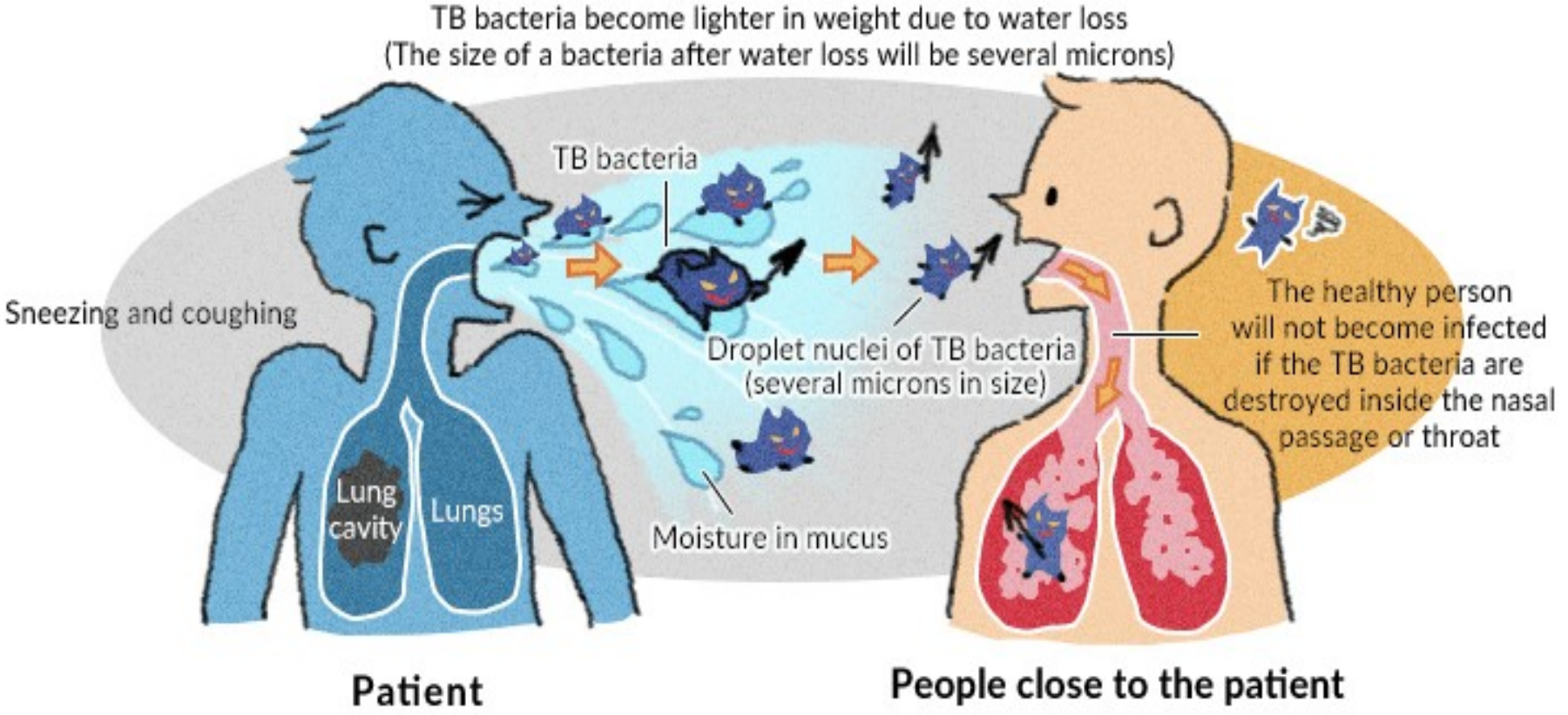


Japan Anti-Tuberculosis Association:Common sense of Tuberculosis 2007,2,2007

Journal of
Applied Microbiology

Journal of Applied Microbiology ISSN 1364-5072

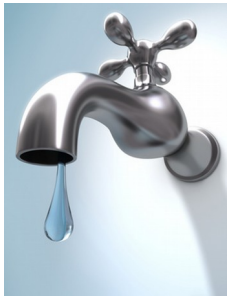
REVIEW ARTICLE

Surrounded by mycobacteria: nontuberculous mycobacteria in the human environment

J.O. Falkinham, III

Department of Biological Sciences, Virginia Polytechnic Institute and State University, Blacksburg, Virginia, USA

Journal of Applied Microbiology **107** (2009) 356–367



Ann Microbiol (2014) 64:735–749
DOI 10.1007/s13213-013-0708-8

ORIGINAL ARTICLE

Nontuberculous mycobacteria: an emerging risk in engineered environmental habitats

Rossella Briancesco · Maurizio Semproni · Rosa Paradiso · Lucia Bonadonna

Journal of Applied Microbiology

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Table 3 Factors influencing distribution of mycobacteria in natural and human engineered environments

Factor	Impacts in habitats: Natural habitats	Impacts in habitats: Engineered habitats
Hydrophobicity	Attach to particulates Biofilm formation Concentration at air : water interfaces Hydrocarbon utilization	Attach to surfaces Biofilm formation Antimicrobial resistance Hydrocarbon utilization
Growth at low pH	High numbers in acidic, brown water swamps and boreal (peat) soils	
Humic and fulvic acid growth stimulation	High numbers in acidic, brown water swamps and boreal (peat) soils	Growth in drinking water distribution systems and household plumbing
Temperature resistance	Survive in hot springs	Survive in buildings and home hot water systems

HALLMARKS

Mycobacterium tuberculosis complex

1. **Have no environmental reservoir**
2. **Spreads exclusively from host-to-host**

NTMs

1. **Acquisition from the enviroment**
2. **Are not trasmitted from person-to-person**

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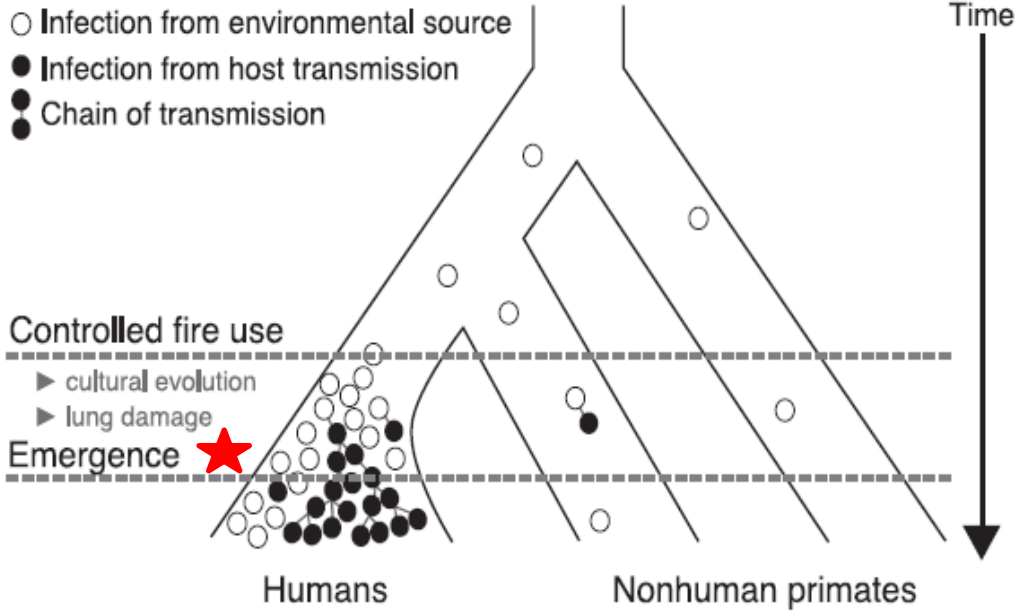
Controlled fire use in early humans might have triggered the evolutionary emergence of tuberculosis

Rebecca H. Chisholm[a,b], James M. Trauer[c], Darren Curnoe[d], and Mark M. Tanaka[a,b,1]

PNAS | August 9, 2016

Tuberculosis (TB) is caused by the *Mycobacterium tuberculosis* complex (MTBC), a wildly successful group of organisms and the leading cause of death resulting from a single bacterial pathogen worldwide. It is generally accepted that MTBC established itself in human populations in Africa and that animal-infecting strains diverged from human strains. However, the precise causal factors of TB emergence remain unknown. Here, we propose that the advent of controlled fire use in early humans created the ideal conditions for the emergence of TB as a transmissible disease. This hypothesis is supported by mathematical modeling together with a synthesis of evidence from epidemiology, evolutionary genetics, and paleoanthropology.



Spatial Clusters of Nontuberculous Mycobacterial Lung Disease in the United States

Jennifer Adjemian[1,2], Kenneth N. Olivier[2], Amy E. Seitz[1,2], Joseph O. Falkinham III[3], Steven M. Holland[2], and D. Rebecca Prevots[1,2]

Measurements and Main Results: We identified seven significant ($P < 0.05$) clusters of PNTM cases. These high-risk areas encompassed 55 counties in 8 states, including parts of California, Florida, Hawaii, Louisiana, New York, Oklahoma, Pennsylvania, and Wisconsin. Five low-risk areas were also identified, which encompassed 746 counties in 23 states, mostly in the Midwest. Counties in high-risk areas were significantly larger, had greater population densities, and higher education and income levels than low-risk counties. High-risk counties also had higher mean daily potential evapotranspiration levels and percentages covered by surface water, and were more likely to have greater copper and sodium levels in the soil, although lower manganese levels.

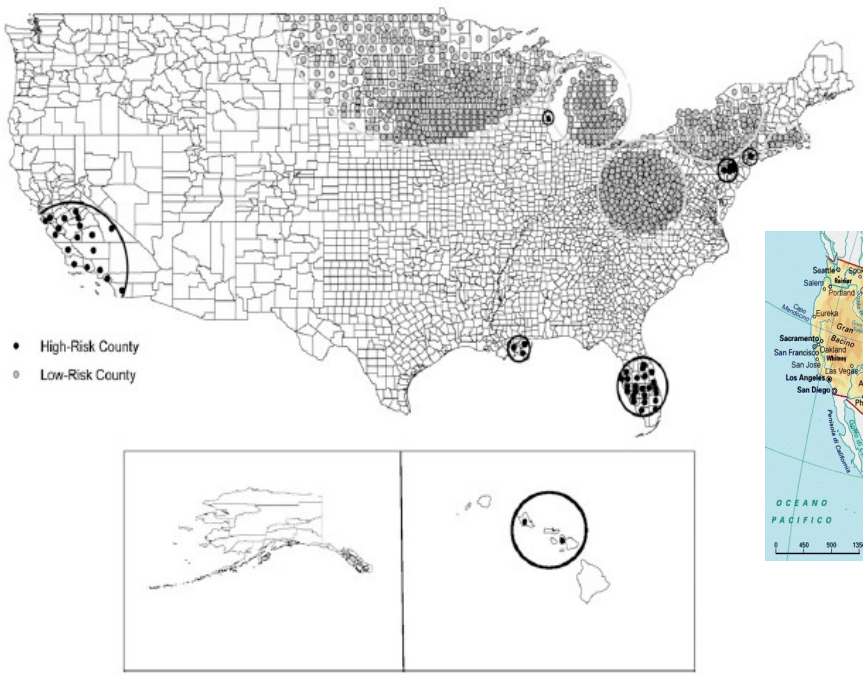


TABLE 1. SUMMARY OF ALL SIGNIFICANT CLUSTERS IDENTIFIED BY SaTScan OF PULMONARY NONTUBERCULOUS MYCOBACTERIAL DISEASE AMONG U.S. MEDICARE BENEFICIARIES 65 YEARS OF AGE AND OLDER

Cluster Type	Centroid County and State	No. of Counties (Radius, km)	Relative Risk	*P* Value
High risk	Highlands, FL	24 (159.4)	1.9	<0.0001
	Santa Barbara, CA	18 (344.5)	2.0	<0.0001
	Montgomery, PA	5 (42.2)	2.2	0.0001
	New York, NY	1 (0)	2.7	0.002
	Milwaukee, WI	1 (0)	3.6	<0.0001
	Kalawao, HI	3 (114.8)	3.7	<0.0001
	Plaquemines, LA	3 (70.2)	6.5	<0.0001
Low risk	Washington, RI	16 (106.7)	0.5	0.02
	Iosco, MI	93 (351.4)	0.4	<0.0001
	Roane, WV	208 (268.5)	0.4	<0.0001
	Polk, MN	247 (689.7)	0.4	<0.0001
	Cayuga, NY	95 (289.0)	0.3	<0.0001

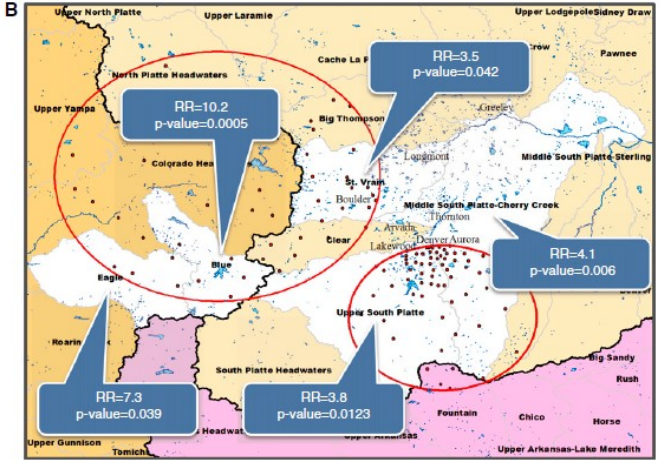


Figure 2. Significant watersheds for all nontuberculous mycobacteria (NTM) species. The four major watersheds in Colorado are represented by four colors: Missouri (*beige*), Upper Colorado (*brown*), Arkansas-White-Red (*purple*), and Rio Grande (*green*). *Black lines* represent watershed boundaries of the four major watersheds. *Black line* separating the Upper Colorado watershed (*brown*) from the remaining three watersheds represents the Continental Divide. Statistically significant watersheds are shown in *white*. (*A*) Four major watersheds are divided into 92 watersheds (boundaries delineated by *gray lines*) in Colorado. Watershed names are printed in boldface type. (*B*) Watersheds narrowed into region of interest. Watershed names are printed in boldface type. Major city names are in printed in *gray*. *Red circles* indicate significant clusters of disease caused by all NTM infections. *Red dots* indicate centroid center of each ZIP code included in the significant cluster. *Blue areas* indicate lakes, reservoirs, and rivers. RR = risk ratio.

A Geospatial Epidemiologic Analysis of Nontuberculous Mycobacterial Infection: An Ecological Study in Colorado

Ettie M. Lipner[1,2], David Knox[3], Joshua French[4], Jordan Rudman[5], Michael Strong[1,2], and James L. Crooks[6,7]

Conclusions: Our findings provide evidence that water derived from particular watersheds may be an important source of NTM exposure in Colorado. The watershed with the greatest risk of NTM disease contains the Dillon Reservoir. This reservoir is also the main water supply for major cities located in the two watersheds with the second and third highest disease risk in the state, suggesting an important possible source of infection.

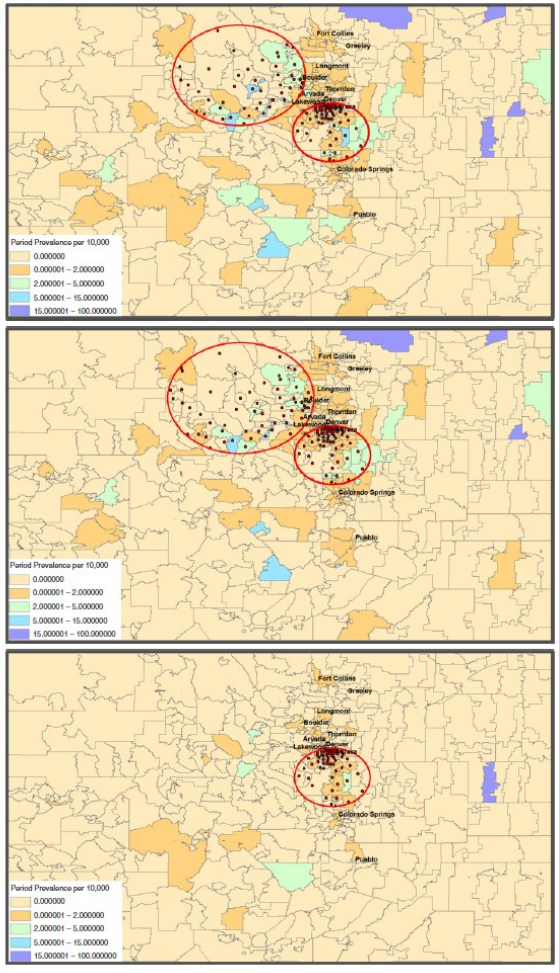


Figure 1. Period prevalence per 10,000 population and significant high-risk clusters of nontuberculous mycobacteria (NTM) disease in Colorado. *Gray lines* delineate ZIP code boundaries throughout the state. *Red circles* indicate significant clusters. *Red dots* indicate centroid center of each ZIP code included in the significant cluster. (*A*) All NTM species. (*B*) Slowly growing NTM species. (*C*) Rapidly growing NTM species.

Infection Sources of a Common Non-tuberculous Mycobacterial Pathogen, *Mycobacterium avium* Complex

Yukiko Nishiuchi[1], Tomotada Iwamoto[2] and Fumito Maruyama[3]**

[1] Toneyama Institute for Tuberculosis Research, Osaka City University Medical School, Toyonaka, Japan, [2] Department of Infectious Diseases, Kobe Institute of Health, Kobe, Japan, [3] Section of Microbiology, Graduate School of Medicine and Faculty of Medicine, Kyoto University, Kyoto, Japan

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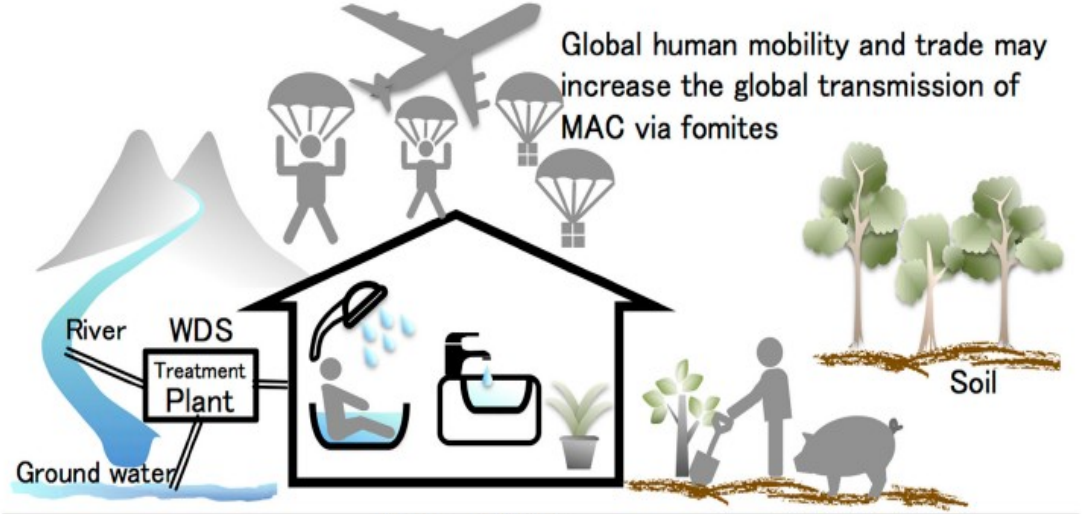
March 2017 | Volume 4 | Article 27



Respiratory Outbreak of *Mycobacterium abscessus* Subspecies *massiliense* in a Lung Transplant and Cystic Fibrosis Center

Moira L. Aitken, M.D.
Ajit Limaye, M.D.
Paul Pottinger, M.D.
Estella Whimbrey, M.D.
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National Institute of Allergy and Infectious Diseases
Bethesda, Maryland
Barbara A. Brown-Elliott, M.S., M.T., S.M.
Steven McNulty, B.S.
Richard J. Wallace, Jr., M.D.
University of Texas Health Science Center
Tyler, Texas

There has been no published report of direct or indirect patient-to-patient respiratory spread of nontuberculous mycobacteria (NTM) (1–5). We report an outbreak of *Mycobacterium abscessus* ss. *massiliense* in five patients with cystic fibrosis (CF). The index case was a 22-year-old man with an FEV_1 of 28% predicted, ΔF508/1717–1G-A, who had *M. abscessus* ss. *massiliense* for 7 years before transfer to our practice, and was 4+ sputum smear–positive for acid-fast bacilli (AFB) at the time of entry into the clinic. Eight months after his transition, four additional patients, aged 27 to 38 years and with FEV_1% of 27 to 44% predicted, all homozygous for ΔF508, were found to have *M. abscessus* ss. *massiliense* in their sputum. All four newly infected patients subsequently had multiple confirmatory positive AFB specimens. Historically all four patients had multiple (five to nine) annual screening mycobacterium sputum samples over the preceding decade. One patient had grown *Mycobacterium avium* complex 8 years previously, and all other samples from all patients had been AFB culture negative.

All patients had *M. abscessus* ss. *massiliense* isolates that were multidrug resistant, including mutational resistance to amikacin and the macrolides; repetitive unit-sequence based polymerase chain reaction pattern and pulsed–field gel electrophoresis analysis of isolates from the five patients were indistinguishable (Figure 1).

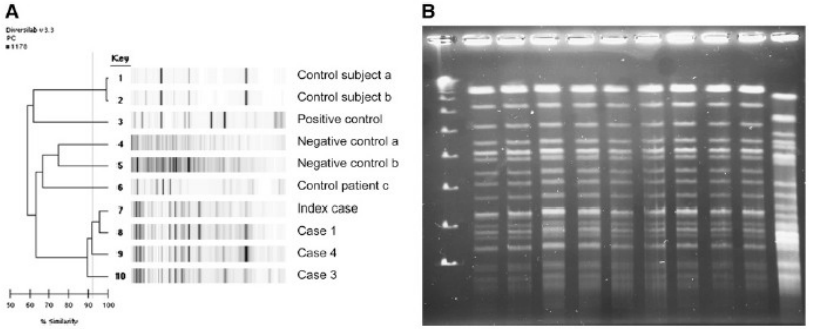


Figure 1. (*A*) Repetitive unit-sequence based polymerase chain reaction pattern from the index case and three of the four outbreak cases with appropriate patient control subjects. Control patient c was the one other patient from the University of Washington cystic fibrosis clinicwho had grown *Mycobacterium abscessus* on annual AFB sputum samples since 2006. This organism is genetically unrelated to the current outbreak (12). (*B*) Pulsed-field gel electrophoresis of five isolates from the index case (2002–2008) and the four outbreak cases with reference values. Control patient c (*A*) is genetically unrelated. The isolates from the index and outbreak cases are genetically identical. The isolates of the index case over time are also genetically indistinguishable. *Lane 1*, λ Ladder; *lane 2*, case 1; *lane 3*, case 3; *lane 4*, index case in 2002; *lane 5*, index case in 2002; *lane 6*, index case in 2004; *lane 7*, index case in 2007; *lane 8*, index case in 2008; *lane 9*, case 4; *lane 10*, case 2; *lane 11*, ATCC 19,977.

We hypothesize that the high mycobacterial load in the sputum of the index case may have contaminated the clinic environment and facilitated patient-to-patient transmission of *M. abscessus*. Transmission could have occurred by patient-to-patient respiratory spread or by contamination of the clinic or some clinic equipment.

This is the first known outbreak of respiratory *M. abscessus* disease occurring in a population of patients with CF (6–11). We strongly advocate rigorous, diligent, repeated surface cleaning and consideration to use airborne isolation rooms when caring for patients whose sputum harbors this organism.

Whole-genome sequencing to identify transmission of *Mycobacterium abscessus* between patients with cystic fibrosis: a retrospective cohort study

thelancet.com Vol 381 May 4, 2013

Josephine M Bryant, Dorothy M Grogono*, Daniel Greaves, Juliet Foweraker, Iain Roddick, Thomas Inns, Mark Reacher, Charles S Hawo Martin D Curran, Simon R Harris, Sharon J Peacock, Julian Parkhill, R Andres Floto*

Method Whole genome sequencing and antimicrobial susceptibility testing were done on 168 consecutive isolates of *M abscessus* from 31 patients attending an adult cystic fibrosis centre in the UK between 2007 and 2011. In parallel, we undertook detailed environmental testing for NTM and defined potential opportunities for transmission between patients both in and out of hospital using epidemiological data and social network analysis.

Findings Phylogenetic analysis revealed two clustered outbreaks of near-identical isolates of the *M abscessus* subspecies *massiliense* (from 11 patients), differing by less than ten base pairs. This variation represents less diversity than that seen within isolates from a single individual, strongly indicating between-patient transmission. All patients within these clusters had numerous opportunities for within-hospital transmission from other individuals, while comprehensive environmental sampling, initiated during the outbreak, failed to detect any potential point source of NTM infection. The clusters of *M abscessus* subspecies *massiliense* showed evidence of transmission of mutations

The finding of frequent *M abscessus* subsp *massiliense* transmission in patients with cystic fibrosis raises several important questions about current infection control measures used in treatment centres, the potential for cross-infection in other patient groups and with other NTM species, and whether mandatory notification of infections with *M abscessus* complex and routine whole genome sequencing might be required to identify and control the spread of these organisms.

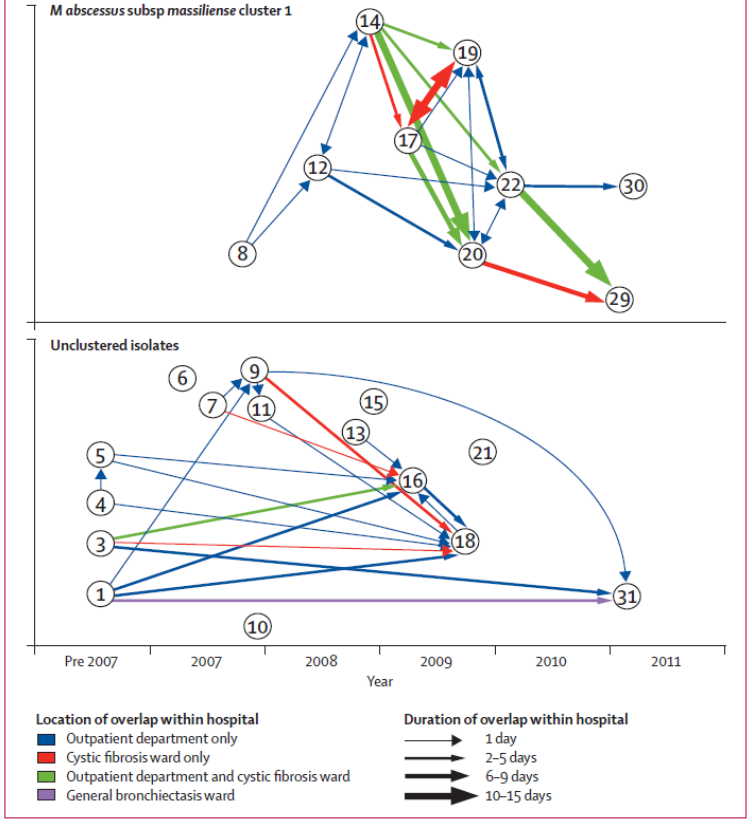


Figure 4: **Network analysis of patients with clustered and non-clustered *M abscessus***
Social network analysis of individuals within *M abscessus* subsp *massiliense* cluster 1 (clustered cases; n=9) were compared with patients with unclustered *M abscessus* isolates (reference cases; n=15). We assumed that patients might acquire infection any time during a 12 month period before their first positive sample and might transmit infection at any time from this point onwards. Arrow thickness denotes duration of overlap within different areas of the hospital for individuals during periods of potential acquisition of infection with potentially infected patients. Arrow direction indicates potential route of transmission. The position of the circles represents the date of the first positive culture for *M abscessus*. Clustered cases were more tightly interconnected (having higher network densities) than references cases, were all exposed to individuals who had the potential to transmit infection during periods of potential acquisition, and that potential transmission events between them occurred both within the outpatients department and/or cystic fibrosis inpatient ward.

FRAMEWORK TOWARDS

TB ELIMINATION

IN LOW-INCIDENCE COUNTRIES

ERS EUROPEAN RESPIRATORY SOCIETY every breath counts

World Health Organization

TB SITUATION IN LOW-INCIDENCE COUNTRIES

TB is a major **global public health problem** that predominantly affects low- and middle-income countries. However, although incidence is lower, it is also a **persistent health threat in high-income countries**, especially among the poorest and in the most vulnerable population.

In 2012, **155 000 people fell ill with TB** in low-incidence countries, and there were **10 000 deaths (30 TB deaths a day).**

15 000 people with TB may be missed each year by health systems in these countries and therefore may not get the TB care that they need and deserve.

The TB situation in most low-incidence countries is characterised by: **low rate of transmission** in the general population; **outbreaks**; majority of people with TB fall ill because of progression of **latent TB infection* (LTBI)**; high degree of concentration in **groups at risk**; and challenges posed by **cross-border migration.**

COUNTRIES WITH LOW TB INCIDENCE

***Low-incidence countries* and territories** are defined as those with a TB notification rate of ≤100 cases (all forms) per million population a year. There are 33 countries[y] and territories in this category today: Australia, Austria, Bahamas, Belgium, Canada, Costa Rica, Cuba, Cyprus, Czech Republic, Denmark, Finland, France, Germany, Greece, Iceland, Ireland, Israel, Italy, Jamaica, Jordan, Luxembourg, Malta, Netherlands, New Zealand, Norway, Puerto Rico, Slovakia, Slovenia, Sweden, Switzerland, United Arab Emirates, United States of America, West Bank and Gaza Strip.

Epidemiology of tuberculosis in big cities of the European Union and European Economic Area countries

G de Vries[1,2], R W Aldridge[3], J A Caylà[4], W. H. Haas[5], A Sandgren[6], N A van Hest[7], I Abubakar (i.abubakar@ucl.ac.uk)[8,9], the Tuberculosis in European Union Big Cities Working Group[10]

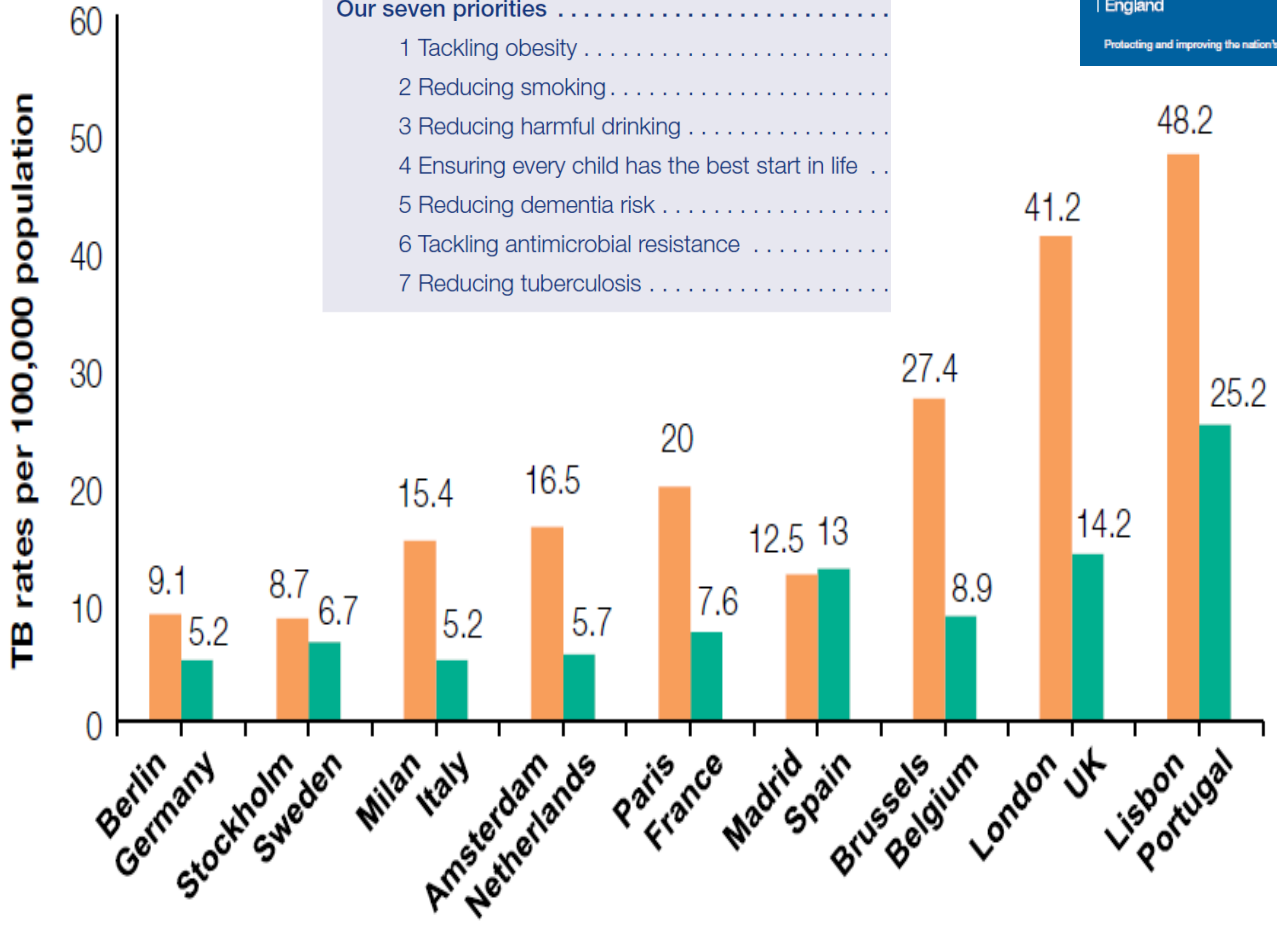
Country	Population	TB cases	Notification rate	Big city	Population	TB cases	Notification rate	Rate ratio[a]
Low-incidence countries (TB incidence <20 per 100,000 population)								
Greece	11,260,402	594	5.3	Athens	745,514	91	11.5	2.2
Hungary	10,030,975	1,407	14.0	Budapest	1,695,000	321	18.9	1.4
Italy	60,045,068	4,244	7.1	Rome	2,724,347	487	17.9	2.5
				Milan	1,650,000[c]	327	19.8	2.8
				Naples	963,661	68	7.1	1.0
				Turin	909,538	183	20.1	2.8
				Palermo	659,433	51	7.7	1.1
				Genoa	611,171	87	14.2	2.0
Netherlands	16,485,787	1,157	7.0	Amsterdam	755,605	143	18.9	2.7
				Rotterdam	699,609	128	21.3	3.0
Norway	4,799,252	358	7.5	Oslo	575,475	121	21,0	2.8
Spain	45,828,172	7,592	16.6	Madrid	3,255,944	580	17.8	1.1
				Barcelona	1,455,000	393	27.0	1.6
				Valencia	814,208	177	21.7	1.3
				Seville	703,206	107	15.2	0.9
				Zaragoza	674,317	117	17.4	1.0
				Malaga	568,305	93	16.4	1.0
Sweden	9,256,347	617	6.7	Stockholm	810,120	39	4.8	0.7
				Gothenburg	500,197	49	9.8	1.5
United Kingdom	61,179,256	8,917	14.6	London	7,753,555	3,440	44.4	3.0
				Glasgow	878,135	213	24.3	1.7
				Birmingham	687,700	399	58.0	4.0
				Leeds	787,700	124	15.7	1.1
				Sheffield	547,000	80	14.6	1.0

Public Health England

Protecting and improving the nation's health

Our seven priorities

1 Tackling obesity
2 Reducing smoking
3 Reducing harmful drinking
4 Ensuring every child has the best start in life
5 Reducing dementia risk
6 Tackling antimicrobial resistance
7 Reducing tuberculosis



Tuberculosis

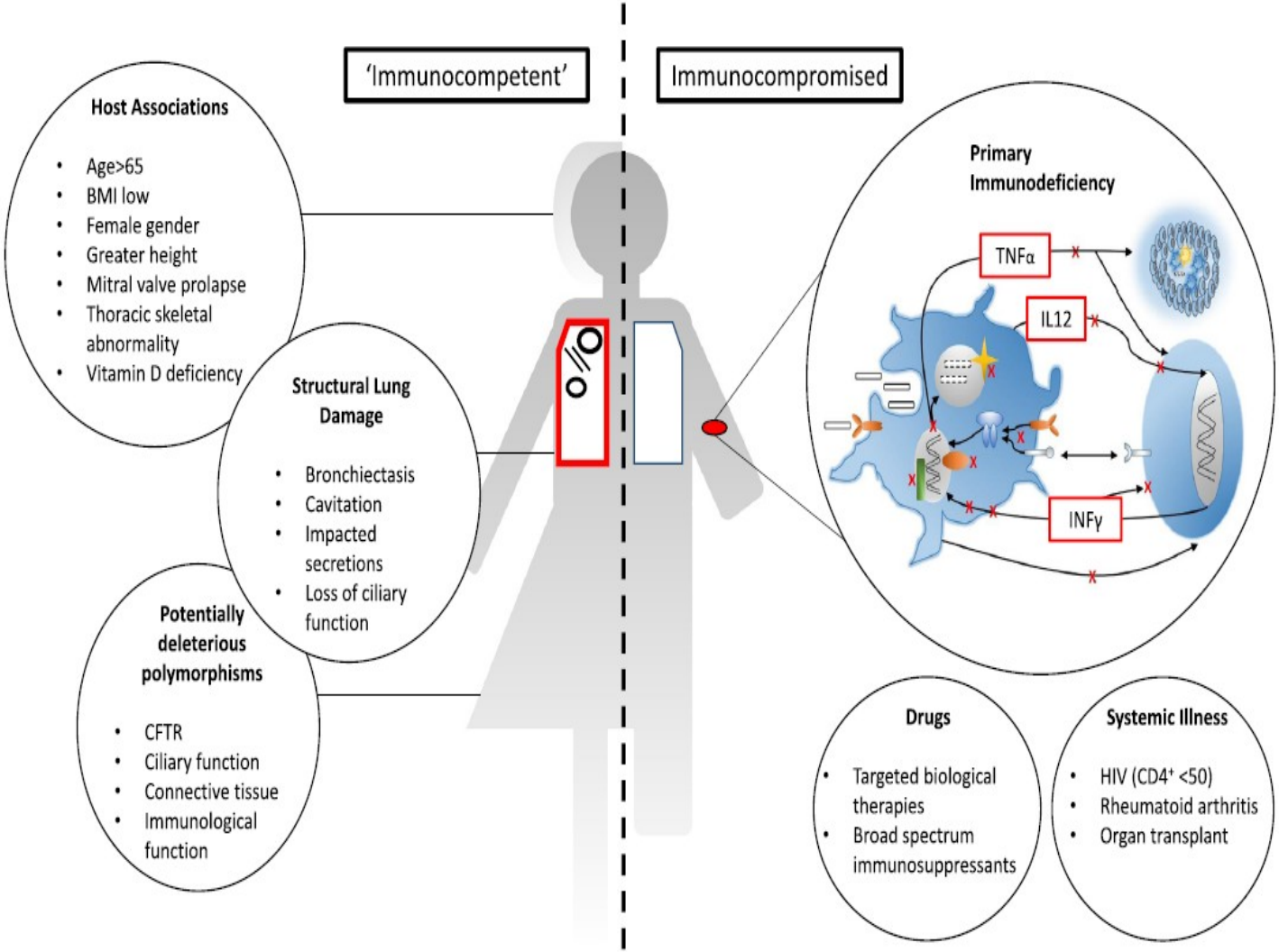
Stephen D Lawn, Alimuddin I Zumla

Lancet 2011; 378: 57-72

	Effect
HIV[5,8]	Greatly increased susceptibility to infection, primary progressive disease, reactivation, and recurrence; disease incidence rate ratio of between 20 and 37 for people infected with HIV depending on country HIV prevalence
Diabetes[9,10]	About three-times increased risk of tuberculosis (especially in insulin-dependent disease); higher mortality
Undernutrition and vitamin deficiencies[11,12]	Undernutrition, low body-mass index, and vitamin D deficiency are each associated with increased risk of tuberculosis disease
Overcrowded living conditions[13]	Increased exposure to infectious cases
Smoking[14-16]	About two-times increased risk of infection, progression to tuberculosis disease and death
Indoor air pollution[15]	About two-times increased risk of disease (weak evidence)
Silicosis[17]	About three-times greater risk in South African gold miners with silicosis
Alcohol[18]	About three-times increased risk of disease associated with consumption >40 g per day
Sex[19]	The ratio of incident tuberculosis disease in men:women is about 2:1 in adults but not children
Age[20]	Major effect on risks of acquisition, disease progression, form of disease, and mortality risk
End-stage renal failure[21]	More than ten-times increased risk
Malignancy[22,23]	Both solid organ and haematological malignancies associated with increased risk
Genetic susceptibility[24]	There is a growing list of genes associated with risk of tuberculosis, including genes for natural resistance-associated macrophage protein 1, interferon γ, nitric oxide synthase 2A, mannan binding lectin, vitamin D receptor, and some Toll-like receptors
TNF antagonist therapy[25,26]	Risk of tuberculosis disease increased about one and a half times in rheumatology patients in North America; risk greater with TNF antibodies than with soluble TNF receptor
Corticosteroid therapy[25]	Risk of tuberculosis disease increased about two times in rheumatology patients in North America

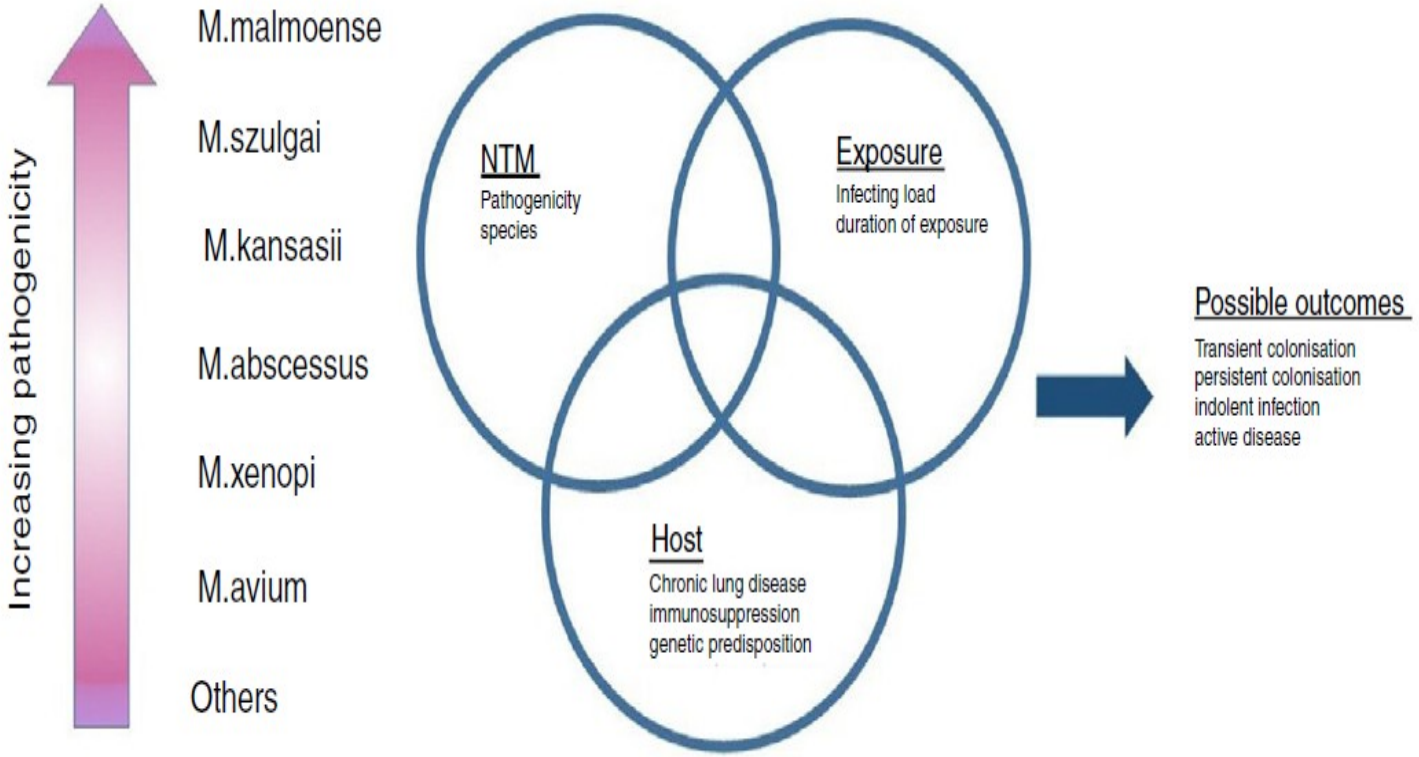
TNF=tumour necrosis factor.

Table: Risk factors associated with tuberculosis


'Immunocompetent'
Immunocompromised
Host Associations
Age>65
BMI low
Female gender
Greater height
Mitral valve prolapse
Thoracic skeletal abnormality
Vitamin D deficiency
Structural Lung Damage
Bronchiectasis
Cavitation
Impacted secretions
Loss of ciliary function
Potentially deleterious polymorphisms
CFTR
Ciliary function
Connective tissue
Immunological function
Primary Immunodeficiency
TNFα
IL12
INFγ
Drugs
Targeted biological therapies
Broad spectrum immunosuppressants
Systemic Illness
HIV (CD4+ <50)
Rheumatoid arthritis
Organ transplant

Non-tuberculous mycobacterial pulmonary infections

Pulmonol. 2018;24(2):120–131



J.D. Chalmers[a,*], T. Aksamit[b], A.C.C. Carvalho[c], A. Rendon[d], I. Franco[e]

Highlight on Advances in Nontuberculous Mycobacterial Disease in North America

Mehdi Mirsaeidi,[1] Maham Farshidpour,[2] Mary Beth Allen,[3] Golnaz Ebrahimi,[1] and Joseph O. Falkinham[4]

[1] Section of Pulmonary, Critical Care, Sleep and Allergy, Department of Medicine M/C 719, University of Illinois at Chicago, 840 S. Wood Street, Chicago, IL 60612-7323, USA
[2] Institute of Human Virology, University of Maryland School of Medicine, Baltimore, MD 21201, USA
[3] Department of Health, University of Louisville, Louisville, KY 40202, USA
[4] Department of Biological Science, University of Virginia Tech, Blacksburg, VA 24061, USA

Hindawi Publishing Corporation
BioMed Research International
Volume 2014, Article ID 919474,

5 categories of susceptible persons for NTM have been identified :

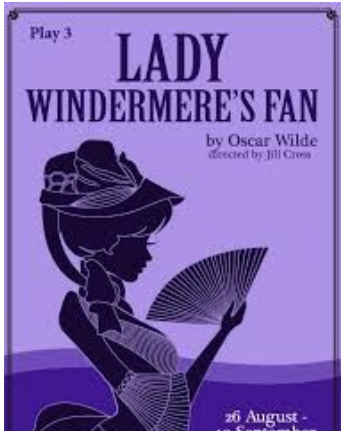
1. **Structural or preexisting pulmonary diseases (COPD, cystic fibrosis,asthma,bronchiectasis)**

2. **Patients with autoimmune disorders who are being treated with anti-TNFα**

3. **HIV+ ed immunodepressi**

4. **Patients with genetic syndromes involving mutations in the IL12 or interferon γ pathways**

5. **Non-smoker, elderly females with a slender body and some characteristics features as scoliosis, pectus defects or mitrale valve prolapsed.**

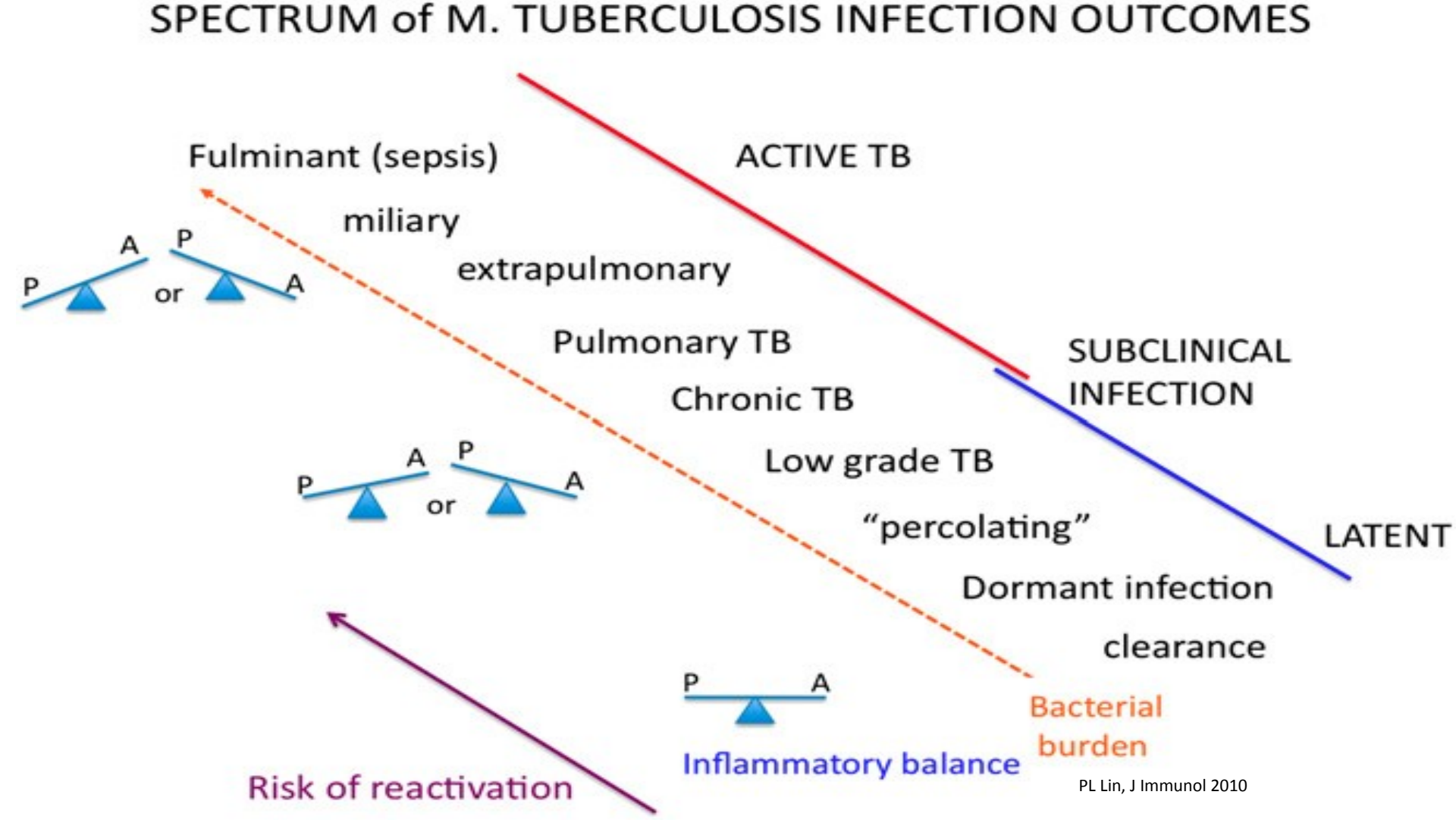


MST1R mutation as a genetic cause of Lady Windermere syndrome

Eur Respir J 2017

MST1R is highly expressed on airway epithelial cells and increases mucociliary function, *i.e.* binding and activation of MST1R by its ligand macrophage-stimulated protein leads to a significant increase of the ciliary beat frequency [14]. Thus, a defect in the mucociliary transport due to a *MST1R* mutation could lead to impaired clearance of NTM, resulting in a vicious cycle of airway inflammation and infection leading to the bronchiectasis typically seen in patients with pNTM. These genetic findings are consistent with the study showing that adult patients with pNTM and without known predisposing factors have reduced ciliary beat frequency [11]. Thus, defects in MST1R function can specifically attenuate IFN-γ production as well as decrease airway ciliary function, with both defects increasing susceptibility to pNTM. The decrease in IFN-γ production was specific for the stimulation with live *M. avium*, since blocking MST1R did not decrease IL-12+IL-18-induced IFN-γ production. The reason for this phenomenon is not known; it might be speculated that *M. avium* has a direct ligand for MST1R.

In conclusion, we have identified rare variants in *MST1R* in four out of 11 pNTM$^{\text{PEX/scoliosis}}$ patients, and suggest that these genetic variants contribute to Lady Windermere syndrome by decreasing airway ciliary function and reducing IFN-γ production in response to NTM.

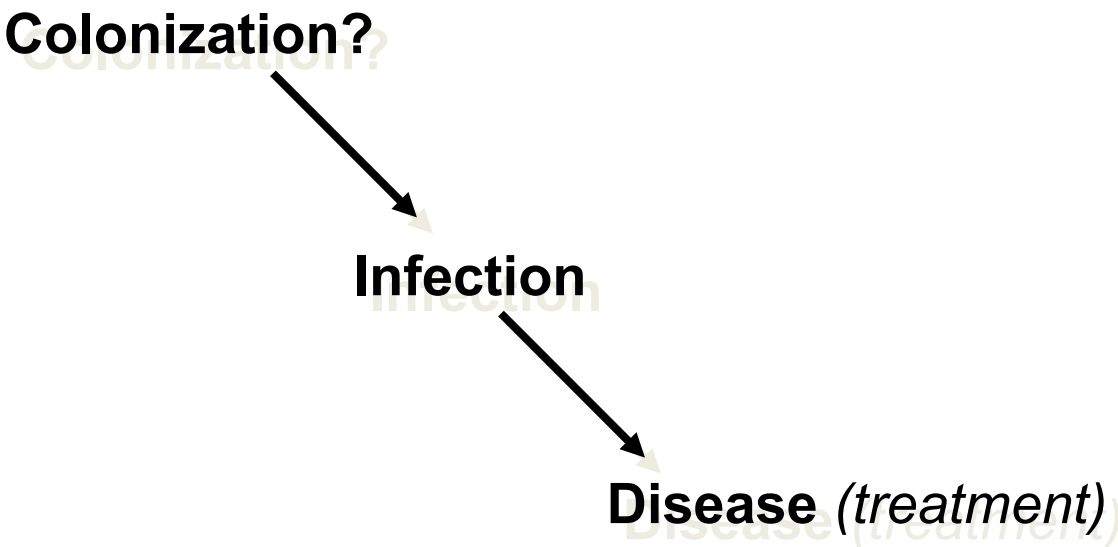


PL Lin, J Immunol 2010

NTM lung disease

Natural History

Diagnosis = Treatment ???



Pulmonary Disease Caused by Non-Tuberculous Mycobacteria

Nasstasja Wassilew[a, b] Harald Hoffmann[c, d] Claire Andrejak[e]
Christoph Lange[a, b, f–h]

Table 1. Wolinsky's clues: support for the diagnosis of NTM-PD [adapted from 75]

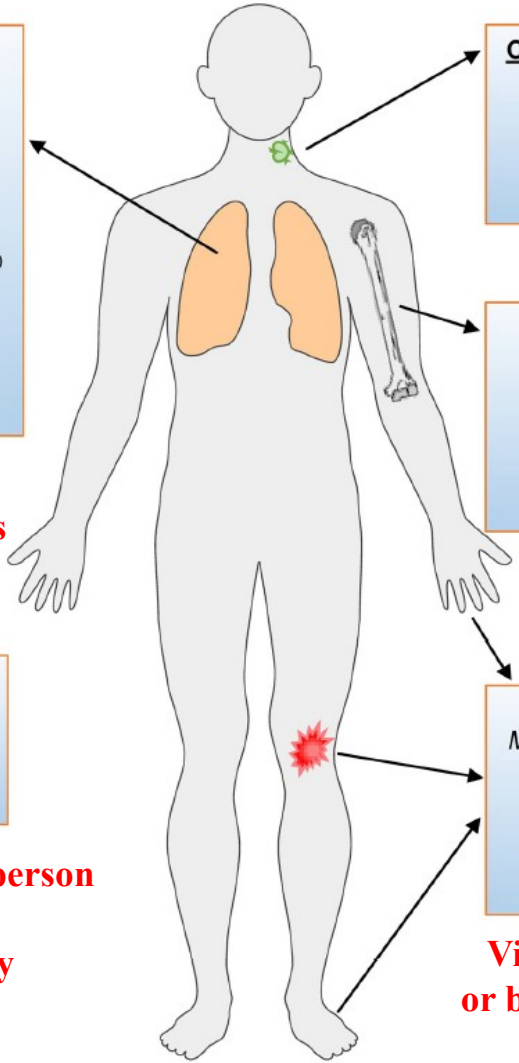
	Clue	Supporting a diagnosis of NTM-PD	Commentary
1	Quantity of growth	Moderate or heavy bacillary growth from sputum or BAL specimen	Relevant to NTM-PD, since moderate or heavy growth of mycobacteria from bronchopulmonary specimens is usually associated with disease
2	Repeated isolation of the same species	Repeated isolation of the same organisms	Single, random isolations often connote contamination; the indication for treatment of NTM-PD should not be based on one unconfirmed isolation of an NTM species
3	Site of positive specimen	Isolation of NTM from a sterile body site, e.g. lung tissue	Less relevant to NTM-PD, since the diagnosis is mostly based on BAL or sputum examinations
4	Identified NTM species	Isolation of *M. abscessus*, *M. kansasii*, and *M. malmoense* from a bronchopulmonary specimen is usually related to PD	*M. gordonae* is among the NTM species most frequently isolated from bronchopulmonary specimens but is almost always not related to NTM-PD; treatment of *M. gordonae* infection should only be initiated if other clues are present
5	Host risk factors	Risk factors for NTM-PD include bronchiectasis, COPD, and other chronic lung diseases	Cave: chronic lung disease also predisposes to colonization with NTM

BAL = Bronchoalveolar lavage.

The complexities and challenges of preventing and treating nontuberculous mycobacterial diseases

Susan L. Baldwin[1], Sasha E. Larsen[1,2], Diane Ordway[3], Gail Cassell[1,4], Rhea N. Coler[1,2,5]*

February 14, 2019
PLOS Neglected Tropical Diseases



Pulmonary
MAC: *M. avium*, *M. intracellulare*, *M. chimaera*
M. kansasii
M. abscessus
M. abscessus sensu stricto
M. massiliense
M. boletti.
M. simiae
M. xenopi
M. malmoense

Inhalation from environmental sources

Cervical Lymphadenitis
M. scrofulaceum
M. avium
M. malmoense
M. lentiflavum
M. bohemicum

Children

Bone and Joints
MAC
M. haemophilum
M. kansasii
M. xenopi
M. goodii
M. terrae complex

Via trauma

Disseminated Infections
M. avium
M. intracellulare
M. haemophilum
M. genavense

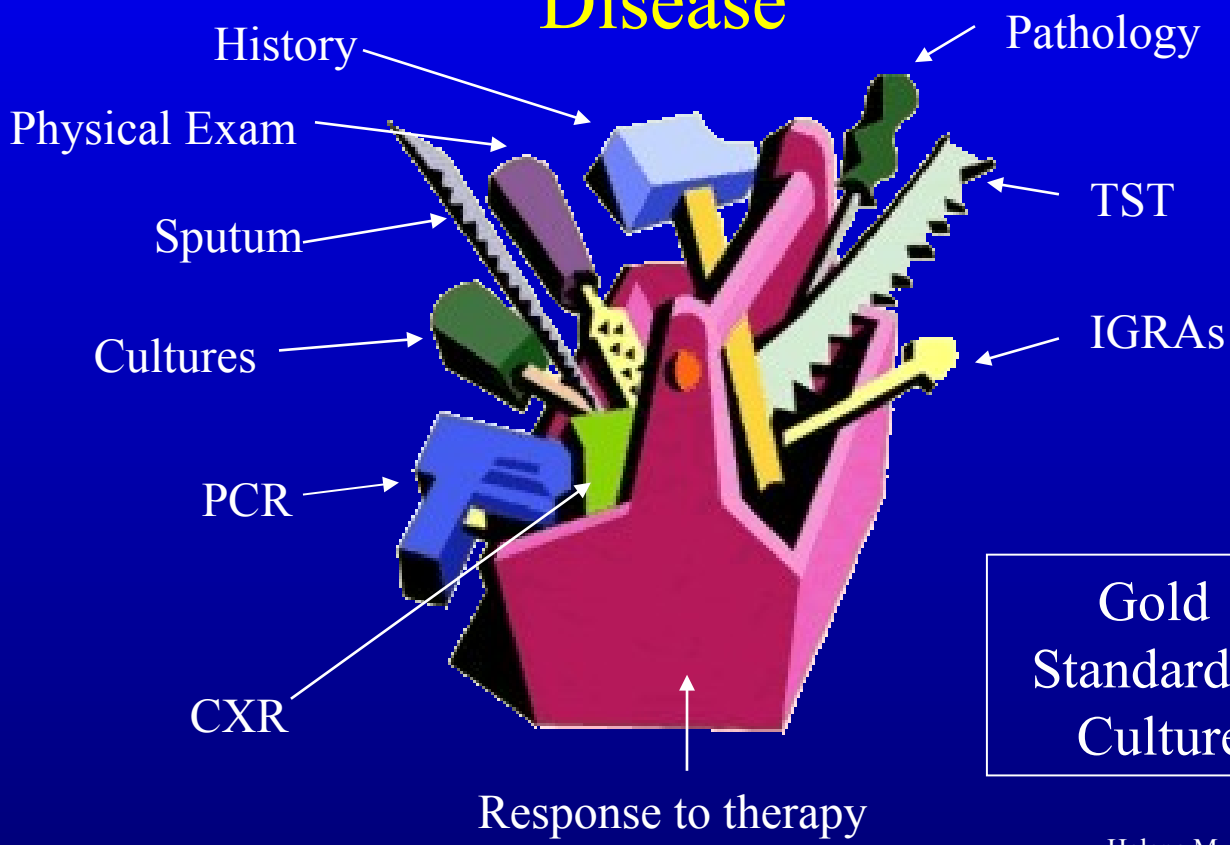
Immunocompromised person
HIV
Anti-TNFa therapy

Skin & Soft Tissue
M. ulcerans (Buruli ulcer)
M. fortuitum
M. marinum
M. haemophilum
M. abscessus
M. chelonae

Via surgery, trauma or broken skin barriers

StopTB Italia © 2012-2014 StopTB Italia Onlus / Tel: +39 [2] 64445886 / 6444332

Toolbox for Diagnosis of TB Disease



Gold Standard = Culture

Helene M. Calvet

RIUNIONE MICOBATTERI ANONIMI

E

SALVE …….
SONO UN NTM……
HO 30 ANNI……

DI ANTIBIOTICI

Current Therapy for Nontuberculous Mycobacterial Pulmonary Disease

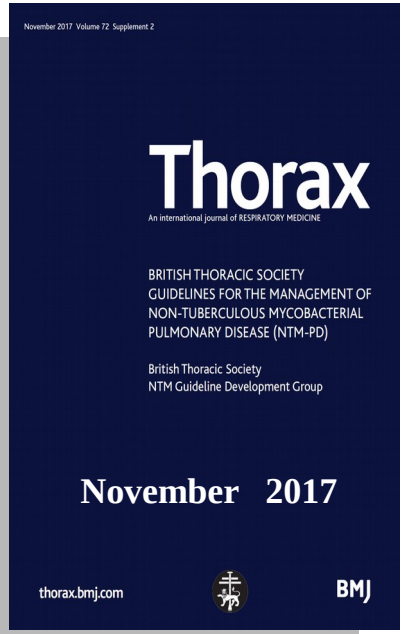
Hilary P. Steele, MD[1]
Lisa M. Brumble, MD[2]
Margaret M. Johnson, MD[1,*]

Curr Treat Options Infect Dis (2015) 7:342–351

Table 1. ATS/IDSA criteria for NTM pulmonary disease

Clinical	1. Pulmonary symptoms AND 2. Appropriate exclusion of other diagnoses
Radiographic	1. Nodular or cavitary opacities on chest radiograph OR 2. High-resolution computed tomography scan that shows multifocal bronchiectasis with small nodules
Microbiologic	1. Positive culture results from at least two separate expectorated sputum samples OR 2. Positive culture result from at least one bronchial wash or lavage OR 3. Transbronchial or other lung biopsy with mycobacterial histopathologic features (granulomatous inflammation or AFB) and one or more sputum or bronchial washings that are culture positive for NTM

CF
CF



SECTION 5: HOW SHOULD THE LUNG DISEASE ATTRIBUTABLE TO NTM INFECTION BE DEFINED?

Recommendation

- In the absence of robust evidence to support an alternative definition and due to the clinical and research benefits of having a uniform definition, use of the American Thoracic Society/Infectious Diseases Society of America (ATS/IDSA) 2007 definition of non-tuberculous mycobacterial (NTM) pulmonary disease is recommended[1] (see Box 1). (Grade D)

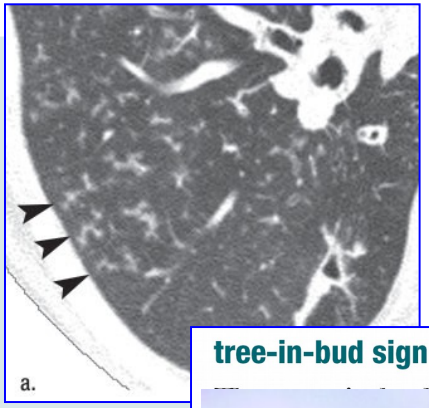
Good practice point

- ✓ The management of coexisting lung conditions/ infections should be optimised before ascribing clinical decline to NTM-pulmonary disease.

NTM causes symptoms similar to a chronic and non-resolving pneumonia. Common symptoms include:

- cough with sputum production,
- tiredness (fatigue),
- fever,
- coughing up blood (hemoptysis)—a late sign of illness,
- unplanned weight loss.

What could be worse than having NTM?
Not knowing you have NTM.



Thin-Section CT of the Secondary Pulmonary Lobule: Anatomy

W. Richard Webb, MD

Radiology

tree-in-bud sign

...ntal unit of ...miniature. ...s, and the ...evel of the ...ronchi- ...nodules its ap-

pearance has been likened to a budding or fruiting tree (67,75) or to the child's toy jacks (103). The term "budding tree" has also been used to describe the appearance of small-airways filling at bronchography (16).

© RSNA, 2006

Dal Piaz

RadioGraphics

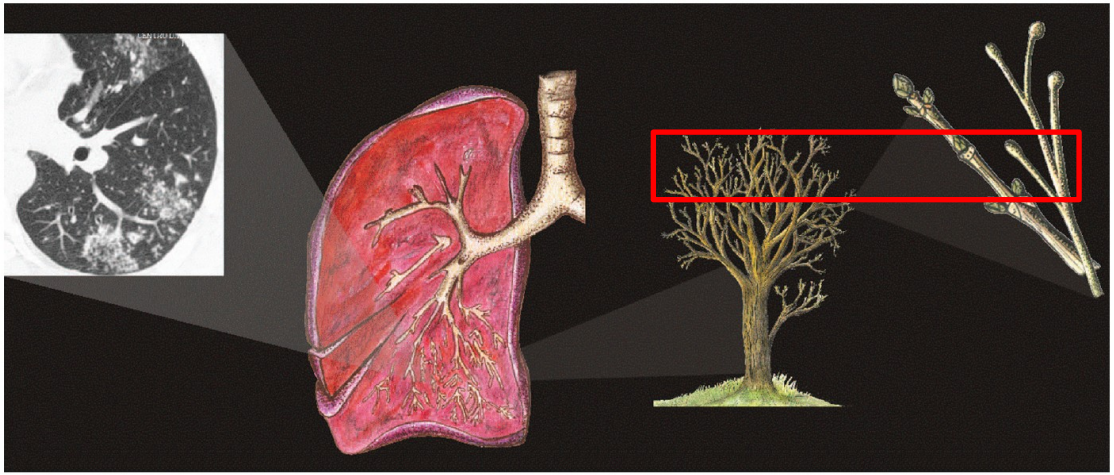


Figure 1. High-resolution CT scan (far left) and drawings of the lung (middle left), a budding tree (middle right), and tree buds (far right) show the tree-in-bud pattern. Note the similarity of the obstructed bronchioles to the objects used in the game of jacks.

Introduction

The "tree-in-bud" pattern at thin-section computed tomography (CT) is characterized by small centrilobular nodules of soft-tissue attenuation connected to multiple branching linear structures of similar caliber originating from a single stalk (Fig 1) (1,2). This pattern also resembles the small objects used in the childhood game of jacks. Initially described in cases of endobronchial spread of *Mycobacterium tuberculosis* (1), it has subsequently been reported as a manifestation of a variety of entities, including peripheral airways

Causes of the Tree-in-Bud Pattern

Peripheral airway disease
- Infection
  - Bacterial
    - *Mycobacterium tuberculosis*
    - *M avium-intracellulare* complex
    - *Staphylococcus aureus*
    - *Haemophilus influenzae*
  - Fungal
    - *Aspergillus*
  - Viral
    - Cytomegalovirus

Radiologic presentation

Three prototypical forms of NTM lung infection.

1) A tuberculosis-like pattern presenting with **infiltrates with or without cavitation** in the upper lobes (mainly among older men with COPD)

2) Presentation with **nodules or nodular bronchiectasis** (in slender older female non smokers – «Lady Windermere syndrome»)

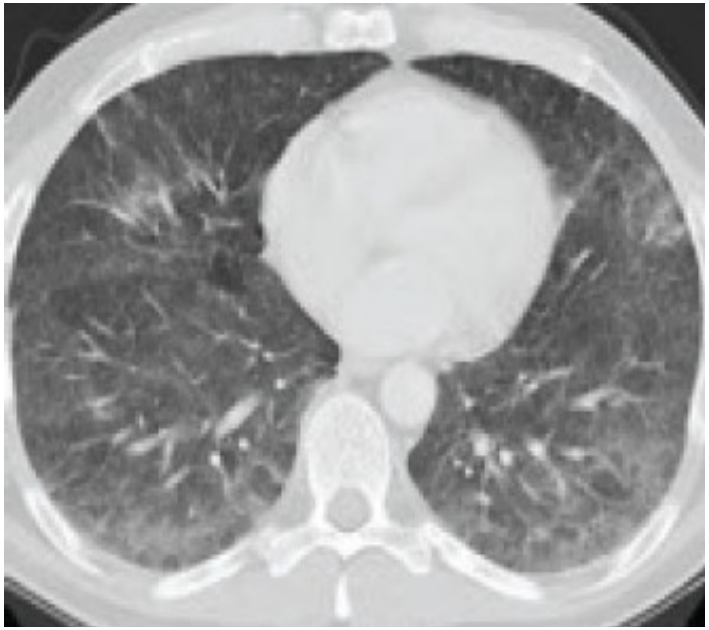
3) A hypersensitivity pneumonitis (associated with exposure to water-containing systems such hot tubs or baths).

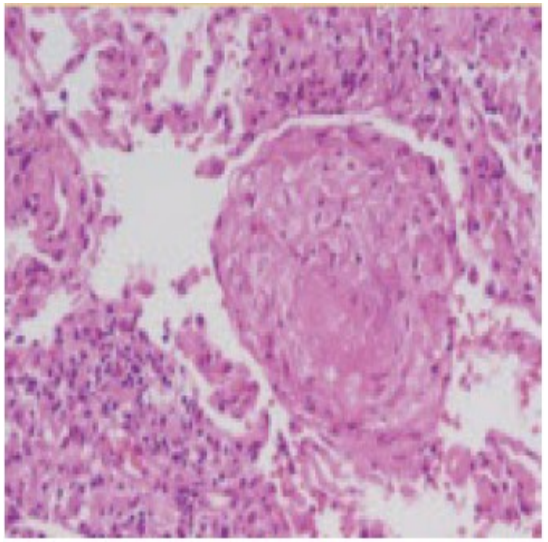
Many patients will have more varied or mixed presentation that do not fit into these prototypic categories.

“Hot tub” lung: Is it on your list of respiratory ailments?

Kevin N. Waninger, MD, and Jill F. Young, DO
Family Medicine Residency Program, St. Luke's Hospital, Bethlehem, Pa

VOL 55, NO 8 / AUGUST 2006 **THE JOURNAL OF FAMILY PRACTICE**





Microscopic evaluation from bronchoscopy revealed noncaseating granulomatous inflammation consistent with hypersensitivity pneumonitis.

Radiology

Yeon Joo Jeong, MD
Kyung Soo Lee, MD
Won-Jung Koh, MD
Joungho Han, MD
Tae Sung Kim, MD
O Jung Kwon, MD

Index terms:
Lung, CT, 60.12111, 60.12115, 60.12118
Lung, diseases, 60.203, 60.2191, 60.26, 60.28
Lung, infection, 60.203

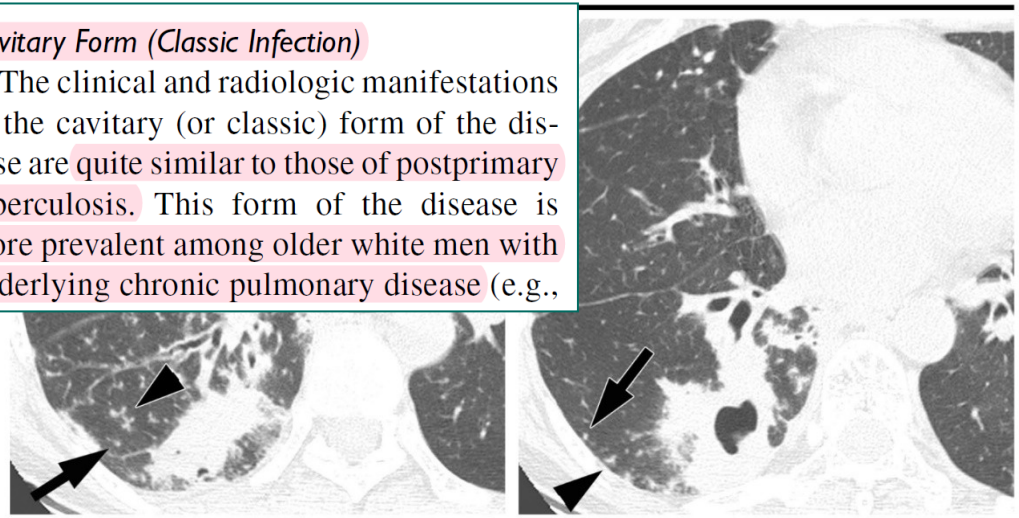
Nontuberculous Mycobacterial Pulmonary Infection in Immunocompetent Patients: Comparison of Thin-Section CT and Histopathologic Findings[1]

Radiology 2004; 231:880–886

Radiology

Cavitary Form (Classic Infection)

The clinical and radiologic manifestations of the cavitary (or classic) form of the disease are quite similar to those of postprimary tuberculosis. This form of the disease is more prevalent among older white men with underlying chronic pulmonary disease (e.g.,



Pulmonary Disease Caused by Non-Tuberculous Mycobacteria

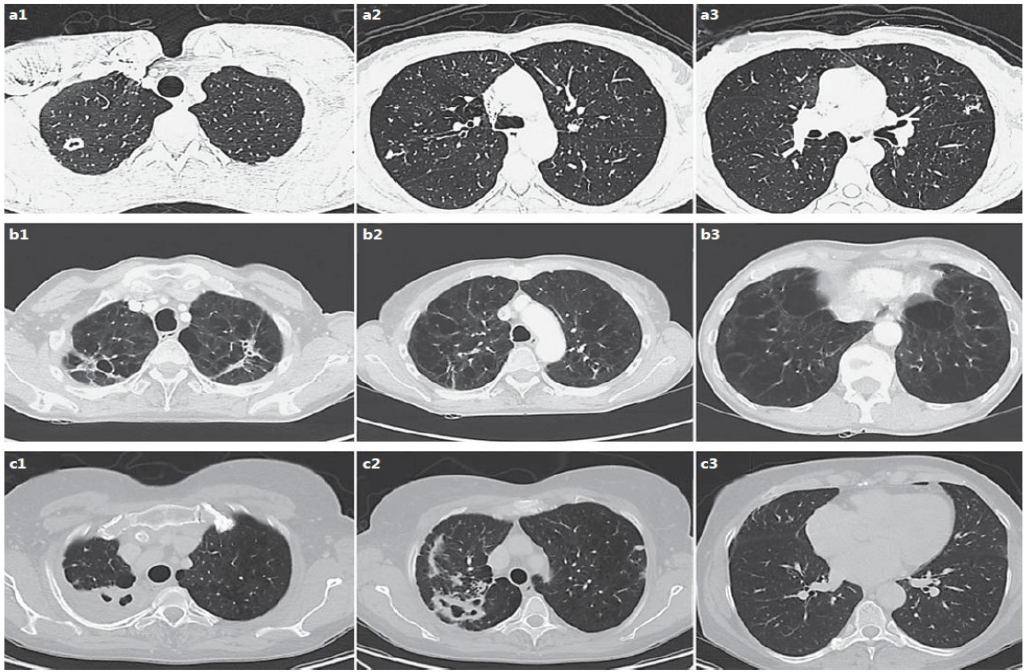
Nasstasja Wassilew[a, b] Harald Hoffmann[c, d] Claire Andrejak[e]
Christoph Lange[a, b, f–h]

Respiration 2016;91:386–402

48 F
Non-Smoking
Pectus
Excavatum
M.Intracellulare

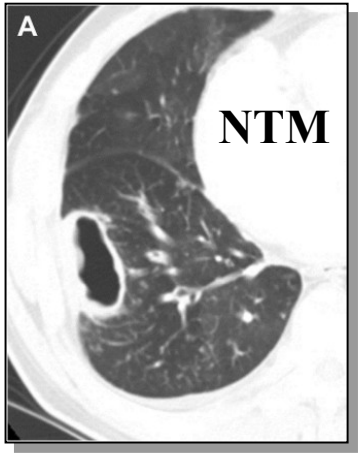
63 M - Smoking
COPD
Gold 3
M.Abscessus

57 F Smoking
COPD
Gold 3
M. Malmoense



PLOS ONE

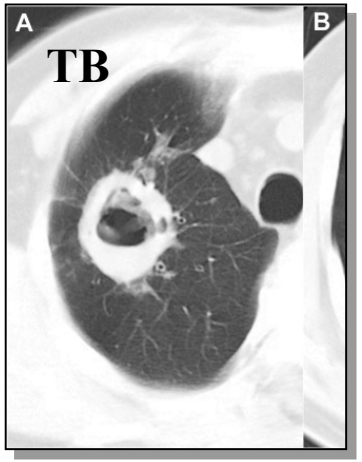
March 27, 2017



RESEARCH ARTICLE

Comparison of chest CT findings in nontuberculous mycobacterial diseases vs. *Mycobacterium tuberculosis* lung disease in HIV-negative patients with cavities

Cherry Kim[1,2], So Hee Park[3], Sang Young Oh[1], Sung-Soo Kim[4], Kyung-Wook Jo[5], Tae Sun Shim[5], Mi Young Kim[1]*



The major cavities in NTM disease generally have thinner and more even walls than those in TB.

Chest X-Ray Finding of Pulmonary Tuberculosis and Nontuberculous Mycobacterial Lung Diseases in Patients with Acid-Fast Bacilli Smear-Positive Sputum

Yuan MK[1,2], Lai YC[3], Chang CY[4] and Chang SC[3,5]*

Table 2: Chest X-ray findings of patients with pulmonary tuberculosis and NTM lung diseases.

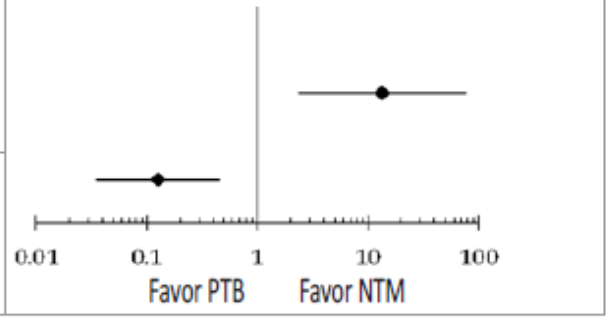
	Pulmonary tuberculosis n=133 (%)	NTM lung disease n=25 (%)	*P* value
Pleural effusion	31 (23.3)	4 (16.0)	0.419
Pleural lesions	23 (17.3)	6 (24.0)	0.409
Fibrothorax	25 (18.8)	3 (12.0)	0.572
Cavity formation	26 (19.5)	1 (4.0)	0.08
Location of cavities			
upper lung zones	23 (88.5)	1 (100.0)	1
middle and lower zones	3 (11.5)	0 (0.0)	
Consalidation	72 (54.1)	5 (20.0)	0.002
Reticulonodular infiltration	116 (87.2)	20 (80.0)	0.349
Honeycombing	5 (3.8)	4 (16.0)	0.036
Military nodules	4 (3.0)	0 (0.0)	1
Atelectasis	59 (44.4)	8 (32.0)	0.251
Mediastinal widening	1 (0.8)	0 (0.0)	1

Chest X-Ray Finding of Pulmonary Tuberculosis and Nontuberculous Mycobacterial Lung Diseases in Patients with Acid-Fast Bacilli Smear-Positive Sputum

Yuan MK[1,2], Lai YC[3], Chang CY[4] and Chang SC[3,5]*

Table 3: Multivariate analysis of predictors for PTB and NTM lung diseases.

Chest X-ray findings	Odds ratio	95% CI
Honeycombing	13.44	2.37 – 76.14
Consolidation	0.13	0.04– 0.45



CI: Confidence Interval; **PTB:** Pulmonary Tuberculosis; **NTM:** Non-Tuberculosis Mycobacterium

Comparative chest computed tomography findings of non-tuberculous mycobacterial lung diseases and pulmonary tuberculosis in patients with acid fast bacilli smear-positive sputum

Mei-Kang Yuan[1,2†], Cheng-Yu Chang[3†], Ping-Huang Tsai[2,4], Yuan-Ming Lee[5], Jen-Wu Huang[6] and Shih-Chieh Chang[2,4*]

Table 3 Multivariate analysis of predictors for NTM lung diseases

CT findings	Odds ratio	95% CI	
Bronchiectasis and cystic changes	33.035	3.010-362.552	Favor NTM
Pleural effusion	0.198	0.038-1.031	Favor PTB
Random nodules	0.074	0.019-0.296	Favor PTB

CI = confidence interval; *PTB* = pulmonary tuberculosis; *NTM* = nontuberculous mycobacterium.

StopTB Italia © 2012-2014 StopTB Italia Onlus / Tel: +39 [2] 64445886 / 64443321 Fax: +39 [2] 64445826 / CF: 97372750154 Indirizzo: viale Zara 81 , 20159 Milano, Italia - www.stc

Microbiological Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease

Jakko van Ingen, MD, PhD

Clin Chest Med 36 (2015) 43–54

CULTURE : is still the mainstay of NTM-PD .

Laboratories should optimize their mycobacterial culture methods to maxime the sensitivity of culture.

The selection of media, use of supplements and incubation temperatures all affect the performance of culture.

MEDIA : The use of a liquid and a solid media, both incubated at 36° to 37°, increases the sensitivity of NTM detection by culture by an average of 15 % (range 0 – 42 %).

An inherent limitation of MGIT is the failure to detect slowly growing microrganisms with very low metabolic activity (es. *Mycobacterium xenopi*)

SUPPLEMENT MEDIA: *Mycobacterium genavense* (to lower pH of the medium);

Mycobacterium haemophilum (requires addition of an iron source)

TEMPERATURE : The optimal growth temperature differs for each NTM species.

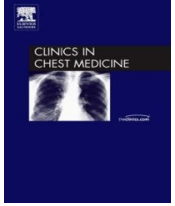
Most species have their growth optimum at 30 °C.

Exceptions: M. abscessus 37 °C; MAC 36 to 42 °C; M. xenopi between 42 and 45 °C. No clear rule for routine incubation at 30 °C; lower respiratory T = 37 °C

Microbiological Diagnosis of Nontuberculous Mycobacterial Pulmonary Disease

Jakko van Ingen, MD, PhD

Clin Chest Med 36 (2015) 43–54



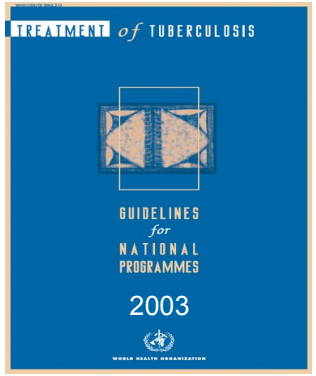
The methods for identification of mycobacteria in clinical laboratories have changed dramatically over the past 2 decades. Currently applied methods and their relative cost are presented in Table 2.

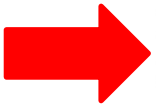
Table 2
Identification methods for nontuberculous mycobacteria

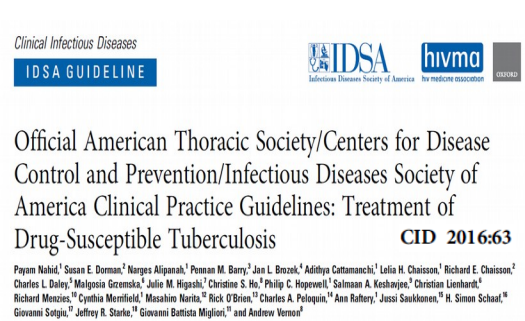
Identification Assay	Discriminatory Power	Relative Cost
HPLC	+	$
Line probe assays	++	$$$
16S rDNA gene sequencing	+++	$$$
Single-gene sequencing (other than 16S rDNA)	++++	$$$
Multigene sequencing	+++++	$$$$
MALDI-TOF	+++	$$

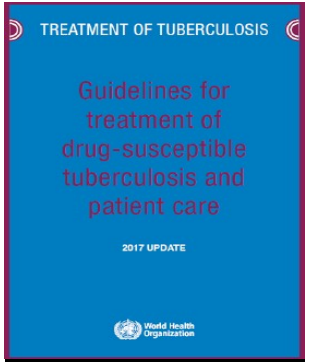
hsp65 – rpoB – 16S-23S ITS

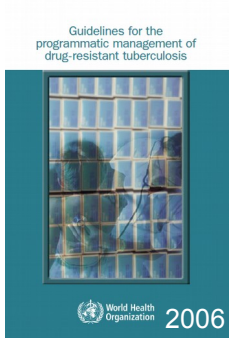
Abbreviations: HPLC, high-performance liquid chromatography; MALDI-TOF, matrix-assisted laser desorption ionization–time-of-flight mass spectrometry.

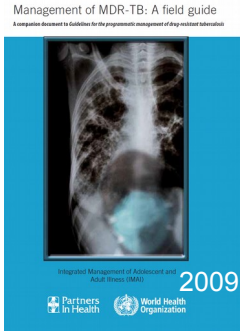

TREATMENT of TUBERCULOSIS
GUIDELINES
for
NATIONAL
PROGRAMMES
2003
WORLD HEALTH ORGANIZATION

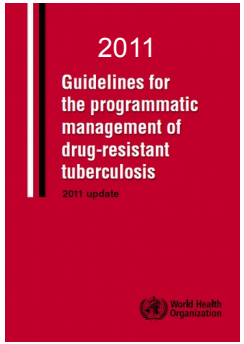


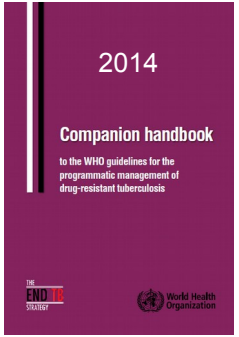

Clinical Infectious Diseases
IDSA GUIDELINE
IDSA
Infectious Diseases Society of America
hivma
hiv medicine association
OXFORD
Official American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America Clinical Practice Guidelines: Treatment of Drug-Susceptible Tuberculosis
CID 2016:63
Payam Nahid,[1] Susan E. Dorman,[2] Narges Alipanah,[3] Pennan M. Barry,[3] Jan L. Brozek,[4] Adithya Cattamanchi,[1] Lelia H. Chaisson,[1] Richard E. Chaisson,[2] Charles L. Daley,[5] Malgosia Grzemska,[6] Julie M. Higashi,[7] Christine S. Ho,[8] Philip C. Hopewell,[1] Salmaan A. Keshavjee,[9] Christian Lienhardt,[6] Richard Menzies,[10] Cynthia Merrifield,[1] Masahiro Narita,[12] Rick O'Brien,[13] Charles A. Peloquin,[14] Ann Raftery,[1] Jussi Saukkonen,[15] H. Simon Schaaf,[16] Giovanni Sotgiu,[17] Jeffrey R. Starke,[18] Giovanni Battista Migliori,[11] and Andrew Vernon[8]

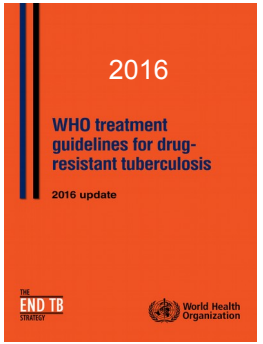

TREATMENT OF TUBERCULOSIS
Guidelines for treatment of drug-susceptible tuberculosis and patient care
2017 UPDATE
World Health Organization


Guidelines for the programmatic management of drug-resistant tuberculosis
World Health Organization
2006


Management of MDR-TB: A field guide
A companion document to Guidelines for the programmatic management of drug-resistant tuberculosis
Integrated Management of Adolescent and Adult Illness (IMAI)
2009
Partners In Health
World Health Organization


2011
Guidelines for the programmatic management of drug-resistant tuberculosis
2011 update
World Health Organization


2014
Companion handbook
to the WHO guidelines for the programmatic management of drug-resistant tuberculosis
THE END TB STRATEGY
World Health Organization


2016
WHO treatment guidelines for drug-resistant tuberculosis
2016 update
THE END TB STRATEGY
World Health Organization

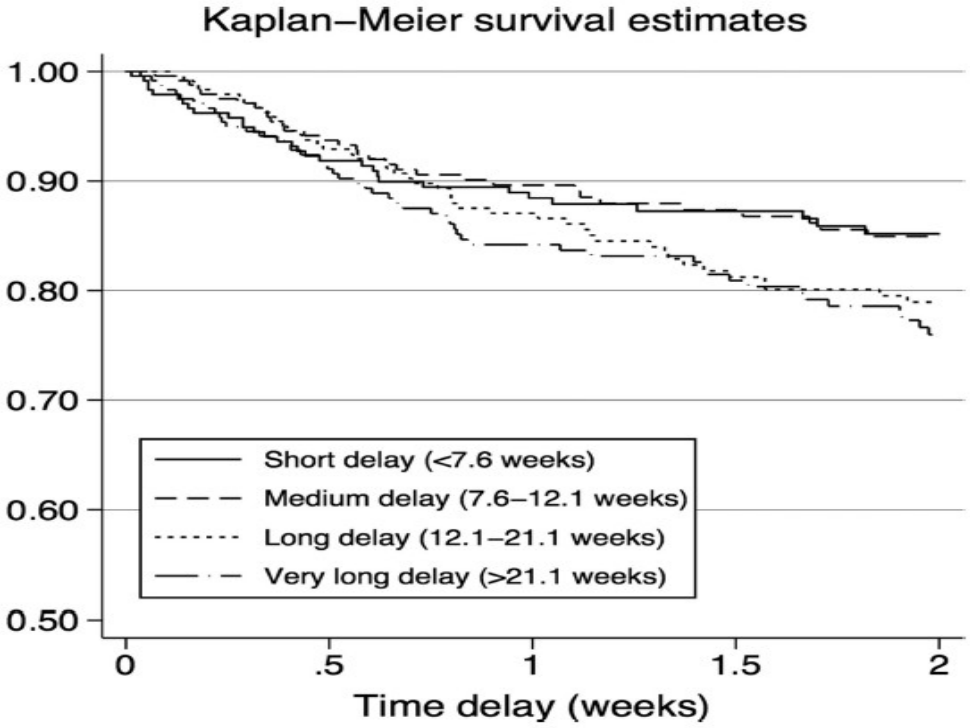
Drug Regimens for Microbiologically Confirmed Pulmonary Tuberculosis Caused by Drug-Susceptible Organisms

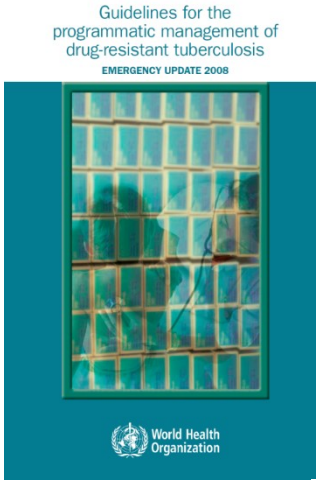
	Intensive Phase		Continuation Phase				
Regimen	Drug[a]	Interval and Dose[b] (Minimum Duration)	Drugs	Interval and Dose[b,c] (Minimum Duration)	Range of Total Doses	Comments[c,d]	Regimen Effectiveness
1	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	7 d/wk for 126 doses (18 wk), or 5 d/wk for 90 doses (18 wk)	182–130	This is the preferred regimen for patients with newly diagnosed pulmonary tuberculosis.	Greater
2	INH RIF PZA EMB	7 d/wk for 56 doses (8 wk), or 5 d/wk for 40 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	110–94	Preferred alternative regimen in situations in which more frequent DOT during continuation phase is difficult to achieve.	
3	INH RIF PZA EMB	3 times weekly for 24 doses (8 wk)	INH RIF	3 times weekly for 54 doses (18 wk)	78	Use regimen with caution in patients with HIV and/or cavitary disease. Missed doses can lead to treatment failure, relapse, and acquired drug resistance.	
4	INH RIF PZA EMB	7 d/wk for 14 doses then twice weekly for 12 doses[e]	INH RIF	Twice weekly for 36 doses (18 wk)	62	Do not use twice-weekly regimens in HIV-infected patients or patients with smear-positive and/or cavitary disease. If doses are missed, then therapy is equivalent to once weekly, which is inferior.	Lesser

Treatment delay affects clinical severity of tuberculosis: a longitudinal cohort study

BMJ Open 2014;**4**:e004818.

J Virenfeldt,[1,2] F Rudolf,[1,2] C Camara,[1] A Furtado,[1] V Gomes,[1] P Aaby,[1,3] E Petersen,[2] C Wejse[1,4]





1.4 Causes of DR-TB

Although its causes are microbial, clinical and programmatic, DR-TB is essentially a man-made phenomenon. From a microbiological perspective, resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. From a clinical and programmatic perspective, it is an inadequate or poorly administered treatment regimen that allows a drug-resistant strain to become the dominant strain in a patient infected with TB. Table 1.1 summarizes the common causes of inadequate treatment.

Short-course chemotherapy (SCC) for patients infected with drug-resistant strains may create even more resistance to the drugs in use. This has been termed the "amplifier effect" of SCC.

MAN-MADE PHENOMENON

TABLE 1.1 **Causes of inadequate antituberculosis treatment** (*1*)

HEALTH-CARE PROVIDERS: INADEQUATE REGIMENS	DRUGS: INADEQUATE SUPPLY OR QUALITY	PATIENTS: INADEQUATE DRUG INTAKE
Inappropriate guidelines	Poor quality	Poor adherence (or poor DOT)
Noncompliance with guidelines	Unavailability of certain drugs (stock-outs or delivery disruptions)	Lack of information
Absence of guidelines	Poor storage conditions	Lack of money (no treatment available free of charge)
Poor training	Wrong dose or combination	Lack of transportation
No monitoring of treatment		Adverse effects
Poorly organized or funded TB control programmes		Social barriers
		Malabsorption
		Substance dependency disorders

World Health Organization

Introduction and rational use of new drugs/regimens for TB treatment

Terapia lunga e complessa

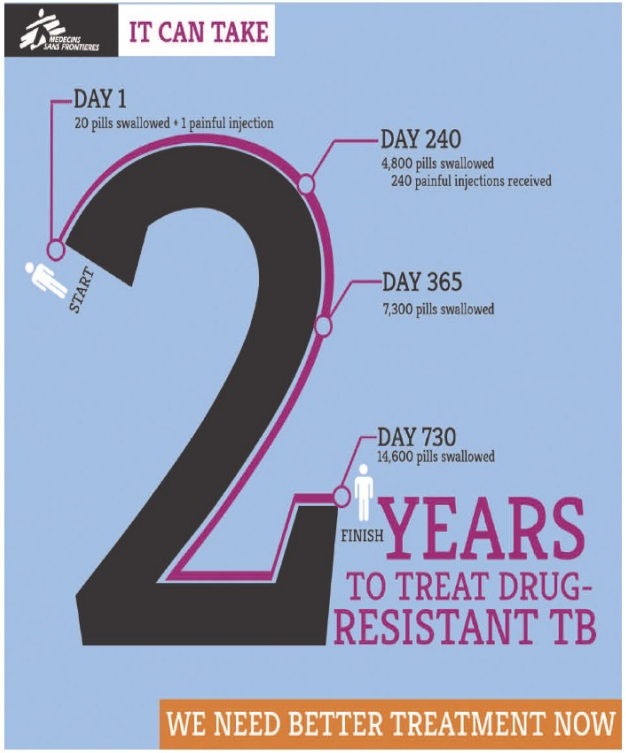
Tossicità

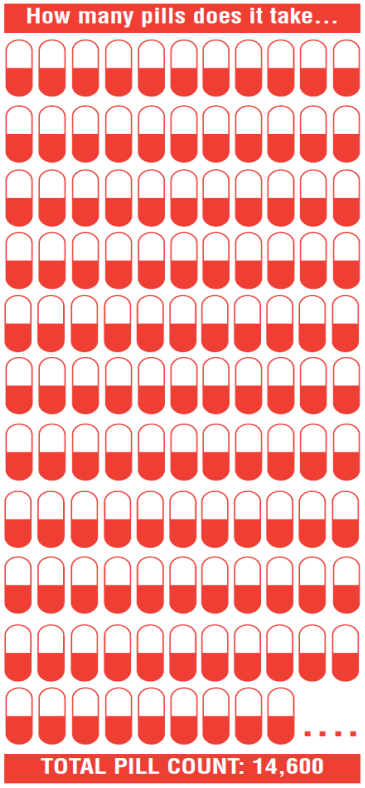
Interazioni farmacologiche

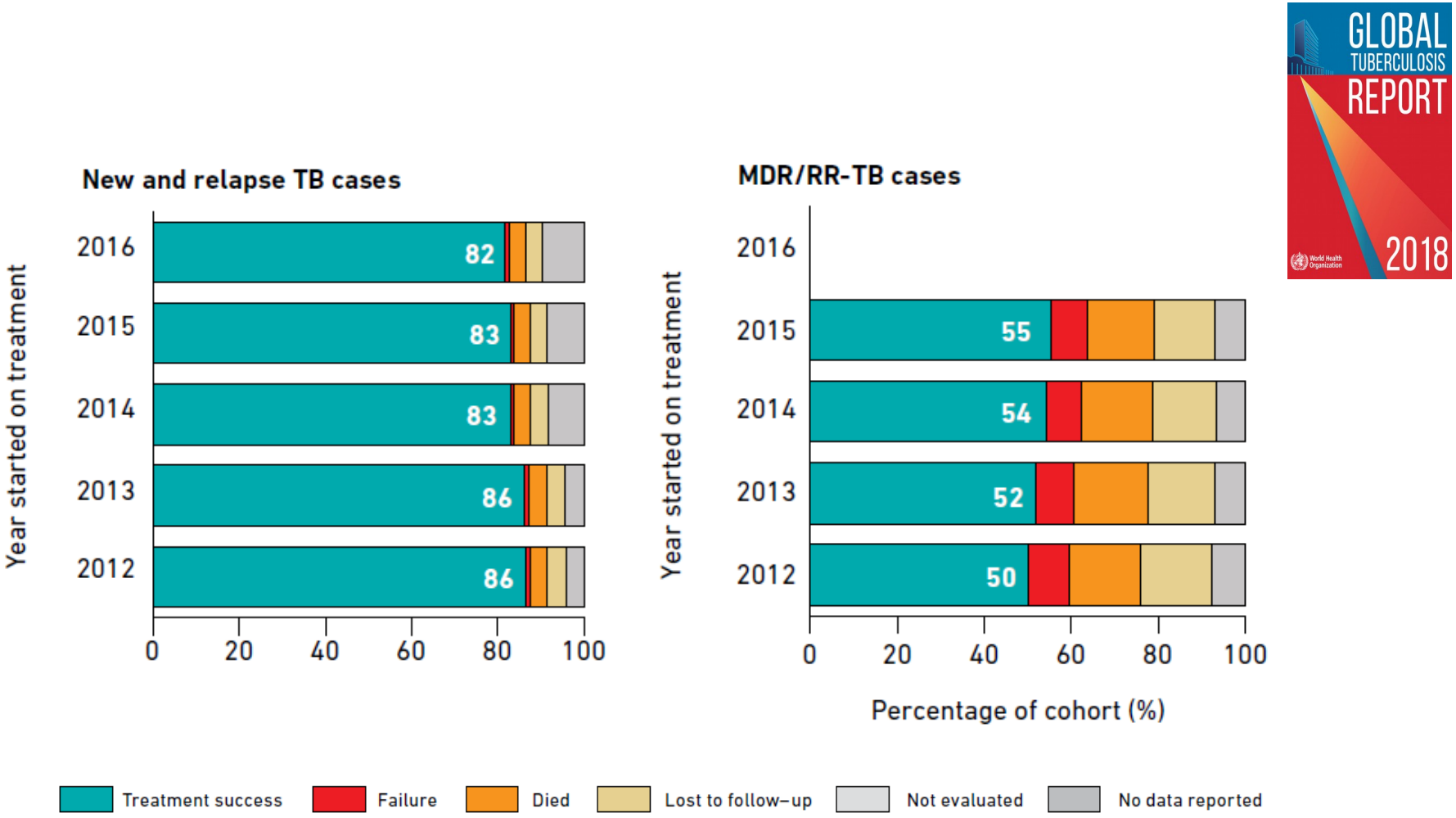
Poco efficace nella TB-MDR

UNMET NEEDS

- **People with drug susceptible TB** need a shorter and simpler therapy;
- **People with drug-resistant TB** need a more efficacious, fully oral, shorter, less toxic and safer therapy;
- **People living with HIV** need TB drugs with no or low drug-drug interactions with antiretrovirals;
- **People with latent TB infection** need shorter and safer therapy;
- **Children with TB** need a more child-friendly and efficacious treatment.

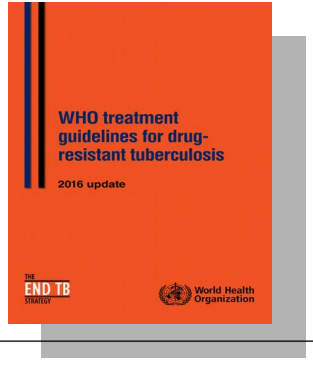

MEDECINS SANS FRONTIERES
IT CAN TAKE
DAY 1
20 pills swallowed + 1 painful injection
DAY 240
4,800 pills swallowed
240 painful injections received
START
DAY 365
7,300 pills swallowed
DAY 730
14,600 pills swallowed
FINISH
2 YEARS
TO TREAT DRUG-RESISTANT TB
WE NEED BETTER TREATMENT NOW


How many pills does it take...
TOTAL PILL COUNT: 14,600


GLOBAL TUBERCULOSIS REPORT 2018
New and relapse TB cases
Year started on treatment
2016
2015
2014
2013
2012
82
83
83
86
86
0
20
40
60
80
100
MDR/RR-TB cases
Year started on treatment
2016
2015
2014
2013
2012
55
54
52
50
0
20
40
60
80
100
Percentage of cohort (%)
Treatment success
Failure
Died
Lost to follow–up
Not evaluated
No data reported

Medicines recommended for the treatment of rifampicin-resistant and multidrug-resistant TB[1]

A. Fluoroquinolones[2]		Levofloxacin Moxifloxacin Gatifloxacin	Lfx Mfx Gfx
B. Second-line injectable agents		Amikacin Capreomycin Kanamycin (Streptomycin)[3]	Am Cm Km (S)
C. Other core second-line agents[2]		Ethionamide / Prothionamide Cycloserine / Terizidone Linezolid Clofazimine	Eto / Pto Cs / Trd Lzd Cfz
D. Add-on agents (not part of the core MDR-TB regimen)	**D1**	Pyrazinamide Ethambutol High-dose isoniazid	Z E H^h
	D2	Bedaquiline Delamanid	Bdq Dlm
	D3	*p*-aminosalicylic acid Imipenem-cilastatin[4] Meropenem[4] Amoxicillin-clavulanate[4] (Thioacetazone)[5]	PAS Ipm Mpm Amx-Clv (T)



FEATURES OF THE SHORTER MDR-TB REGIMEN

- Standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-12 months
- Indicated conditionally in MDR-TB or rifampicin-resistant-TB, regardless of patient age or HIV status
- Monitoring for effectiveness, harms and relapse will be needed, with patient-centred care and social support to enable adherence
- Programmatic use is feasible in most settings worldwide
- Lowered costs (<US$1,000 in drug costs/patient) and reduced patient loss expected
- Exclusion criteria: 2nd line drug resistance, extrapulmonary disease and pregnancy.

REGIMEN COMPOSITION

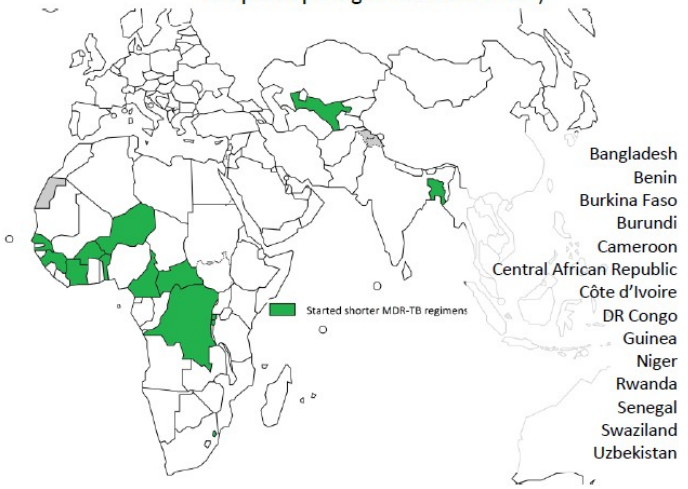
4-6 Km-Mfx-Pto-Cfz-Z-$H_{high\text{-}dose}$-E / 5 Mfx-Cfz-Z-E

Km=Kanamycin; Mfx=Moxifloxacin; Pto=Prothionamide;
Cfz=Clofazimine; Z=Pyrazinamide;
$H_{high\text{-}dose}$= high-dose Isoniazid; E=Ethambutol

World Health Organization

THE SHORTER MDR-TB REGIMEN

Countries using the shorter MDR-TB regimen
(in addition, Ethiopia, South Africa, Viet Nam and Mongolia are participating in the clinical trial)



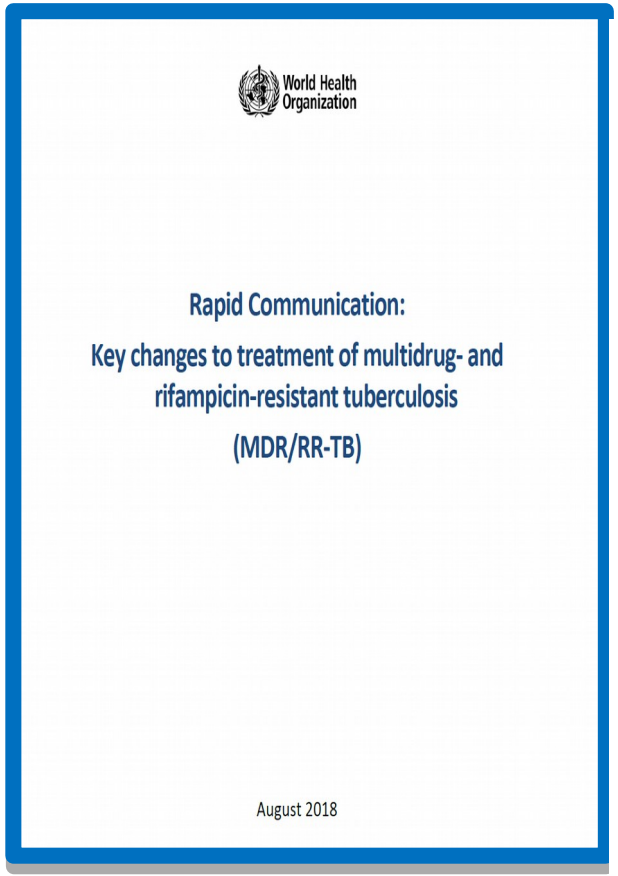


Table 1. Grouping of medicines recommended for use in longer MDR-TB regimens

GROUP	MEDICINE	Abbreviation
Group A: Include all three medicines (unless they cannot be used)	Levofloxacin OR Moxifloxacin	Lfx Mfx
	Bedaquiline[1,4]	Bdq
	Linezolid[2]	Lzd
Group B: Add both medicines (unless they cannot be used)	Clofazimine	Cfz
	Cycloserine OR Terizidone	Cs Trd
Group C: Add to complete the regimen and when medicines from Groups A and B cannot be used	Ethambutol	E
	Delamanid[3,4]	Dlm
	Pyrazinamide[5]	Z
	Imipenem-cilastatin OR Meropenem[6]	Ipm-Cln Mpm
	Amikacin (OR Streptomycin)[7]	Am (S)
	Ethionamide OR Prothionamide	Eto Pto
	p-aminosalicylic acid	PAS

Better data, more tailored tuberculosis therapies

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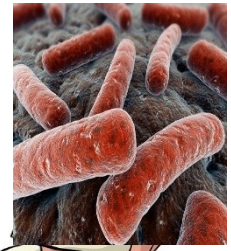
The new WHO-recommended regimen for multidrug-resistant tuberculosis (previously known as Bangladesh regimen), which is expected to increase patients' adherence and programmatic sustainability (being shorter and cheaper), includes pyrazinamide and fluoroquinolones among its core drugs.[12] The variability in drug resistance patterns calls for understanding of national and subnational epidemiology, and emphasises the need for rapid molecular methods and drug susceptibility testing to exclude drug resistance whenever there is suspicion that it might be present. Only with accurate and timely diagnosis will the spread of drug-resistant tuberculosis be contained.

NTM



Trattare o ….non trattare ?

Update on pulmonary disease due to non-tuberculous mycobacteria

Jason E. Stout [a,1,*], Won-Jung Koh [b,1], Wing Wai Yew [c]

International Journal of Infectious Diseases 45 (2016) 123–134

5.1. Treat or not

A diagnosis of NTM lung disease alone does not obligate the immediate initiation of treatment directed against the NTM pathogen. Instead, this decision should be based on the potential risks and benefits of a prolonged course of multiple antibiotics for the individual patient, taking into consideration age, comorbid medical conditions, and disease type.[6,116] Patients with fibrocavitary disease usually require immediate treatment because cavitary disease is associated with a higher rate of mortality due to NTM lung disease.[117,118] Conversely, nodular bronchiectatic disease tends to occur in the absence of significant comorbidity and often progresses slowly.[119] Therefore, early treatment of mild and indolent nodular bronchiectatic disease may not be advisable because of the adverse effects of the long-term use of multiple antibiotics.[6,116] The decision may also be aided by molecular analyses, because specific mycobacterial genotypes have been shown to be predictive of disease progression or treatment response in patients with NTM lung disease.[120,121] Because microbiological cure can be difficult to achieve in a substantial proportion of patients, other treatment goals, including improvement in quality of life, may be more appropriate.[122,123]

CURRENT TREATMENT OPTIONS FOR NTM PULMONARY DISEASE

❖ **NO STANDARDIZED NTM TREATMENT**

❖ **NOT WELL TOLERATED IN SOME PATIENTS**
(Adverse events, Drug-Drug interactions)

❖ **LONG DURATION OF TREATMENT**
(Nonadherence, Treatment discontinuation)

NTM-PD : SITUAZIONE ATTUALE

- **IDSA/ATS Guidelines for NTM 2007**
- **USCFF and ECFS guidelines 2016 (Thorax)**
- **BTS Guidelines for NTM pubblicate Novembre 2017**
- **ERS/ATS Guidelines for NTM in pubblicazione (?)**
- **Recommendation of the German Central Commitee against TB and the German Respiratory Society for the diagnosis and treatment of NTM (Pneumologie 2016)**

Table 1. Key to Evidence Statements

Grade	Evidence
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies or high quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non analytic studies, for example, case reports, case series
4	Expert opinion

RCT: randomised control trial

- **No GRADE A recommendations on treatment**
- **No treatment choices supported by high quality randomized clinical trials**
- **Treatment recommendations for the common NTM species such as M. Avium are GRADE D**

Table 2 Grades of recommendations

Grade	Type of evidence
A	At least one meta-analysis, systematic review, or RCT rated as 1++ and directly applicable to the target population *or*
	A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population and demonstrating overall consistency of results *or*
	Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results or
	Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4 or
	Extrapolated evidence from studies rated as 2+
√	Important practical points for which there is no research evidence, nor is there likely to be any research evidence. The guideline committee wishes to emphasize these as Good Practice Points.

Table 2. Summary of types of antibiotic resistance and associated resistance mechanisms in nontuberculous mycobacteria

Type of resistance	Associated gene or cell component	Mechanism	Antibiotic
Natural resistance	Cell envelope	Low permeability	β-Lactams
	erm gene	Polymorphisms in *erm*	Inducible resistance to macrolides
	Ethambutol resistance-determining region	Polymorphisms in *embB*	Ethambutol
	Quinolone resistance-determining region	Polymorphisms in *gyrA* and *gyrB*	Quinolone
	whiB gene	Presence of *whiB*	Large spectrum of antibiotics
	Efflux pump system	Function of MmpL transporter	Clofazimine, bedaquiline, thiacetazone
Acquired resistance	*rpoB* gene	Mutation of *rpoB*	Rifampin
	23S rRNA gene (*rrl*)	Mutation of *rrl*	Macrolides
	16S rRNA gene (*rrs*)	Mutation of *rrs*	Aminoglycosides

erm, erythromycin ribosomal methylase; *gyr*, subunits of DNA gyrase; *whiB*, transcriptional regulator whiB; MmpL, mycobacterial membrane protein large; *rpoB*, β subunit of bacterial RNA polymerase; rRNA, ribosomal RNA.

StopTB Italia © 2012-2014 StopTB Italia Onlus / Tel: +39 [2] 64445886 / 64443321 Fax: +39 [2] 64445826 / CF: 97372750154 Indirizzo: viale Zara 81 , 20159 Milano, Italia - **www.stoptb.it**

Treatment for Mycobacterium abscessus Pulmonary Disease

Table 3. Antibiotic Therapy Used and Duration of Use

Drug	Percentage of patients who received antibiotic for at least 1 month	Median no. of months of antibiotic use
Azithromycin	77	18
Intravenous amikacin	71	3
Imipenem	55	3
Clarithromycin	49	16.5
Ciprofloxacin	43	12
Cefoxitin	30	3
Inhaled amikacin	28	12
Moxifloxacin	12	12
Clofazimine	9	12.5
Minocycline	6	21.5
Bactrim	4	15
Levofloxacin	4	4
Linezolid	3	5.5
Tigecycline	3	2
Gatifloxacin	1	11
Doxycycline	1	4
Meropenem	1	2

16 different antibiotics were used in 42 different combinations for an average of 4.6 drugs per patient over the course of therapy with a median of 6 intravenous antibiotic months.

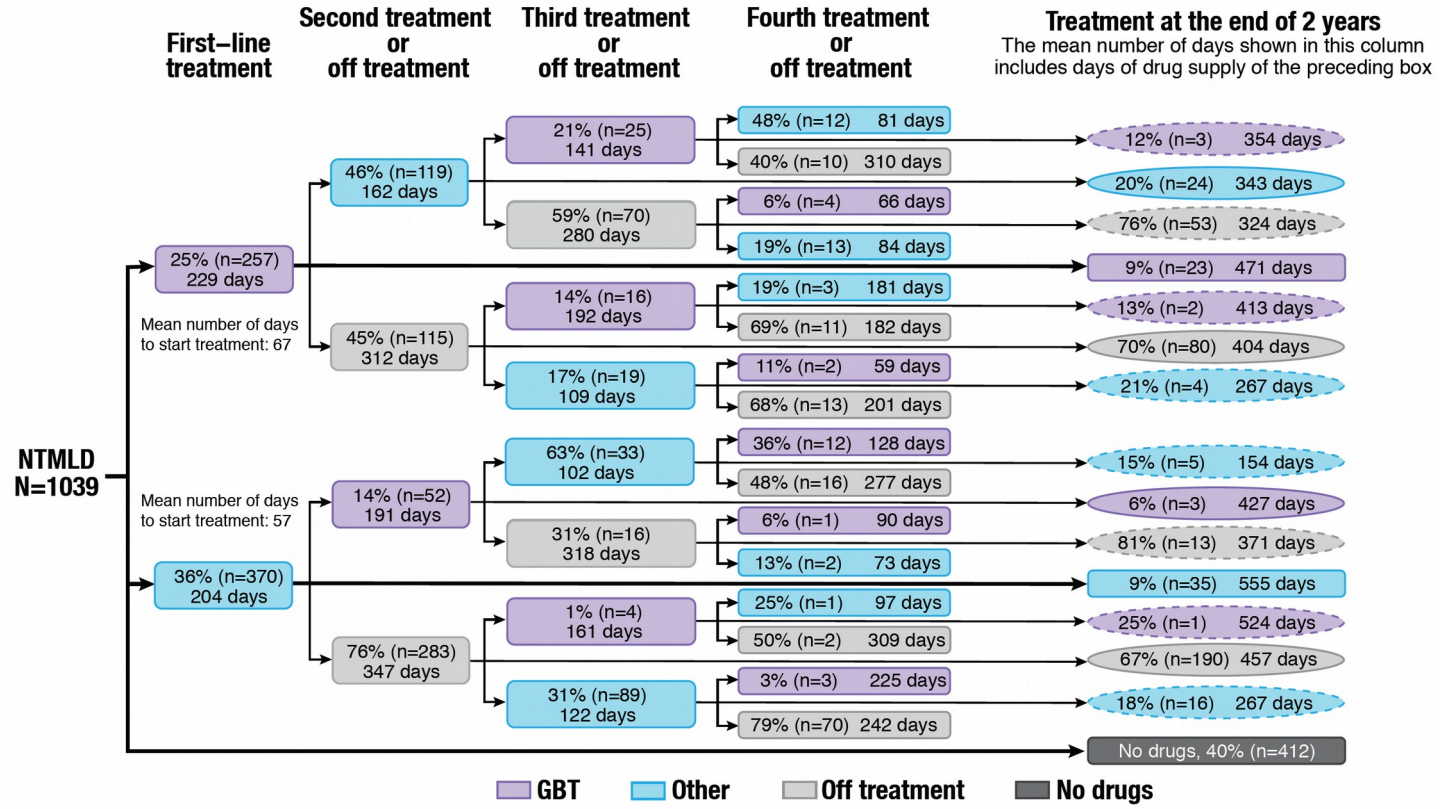
Jarand J et al. CID 2011

Drug Treatment Pathways 2 Years Following Clinical Diagnosis of Nontuberculous Mycobacterial Lung Disease in a Large US Managed Care Population

A.E. O'Donnell,[1] K.N. Olivier,[2] T.K. Marras,[3] J. Adjemian,[4] G. Eagle,[5] X. Li,[6] P. Wang,[5] R. Zhang,[7] and Q. Zhang[5]

[1]Georgetown University Hospital, Washington, DC; [2]Cardiovascular and Pulmonary Branch/National Heart, Lung, and Blood Institute, Bethesda, MD; [3]Toronto Western Hospital, Toronto, ON, Canada; [4]National Institutes of Health, Bethesda, MD; [5]Insmed Inc., Bridgewater, NJ; [6]KMK Consulting Inc., Morristown, NJ; [7]Orbis Data Solutions, Woburn, MA

Figure 2. Treatment Pathways Following NTMLD Diagnosis



Note: Days labeled inside each box indicate the average duration of the drug regimen for patients in the box.

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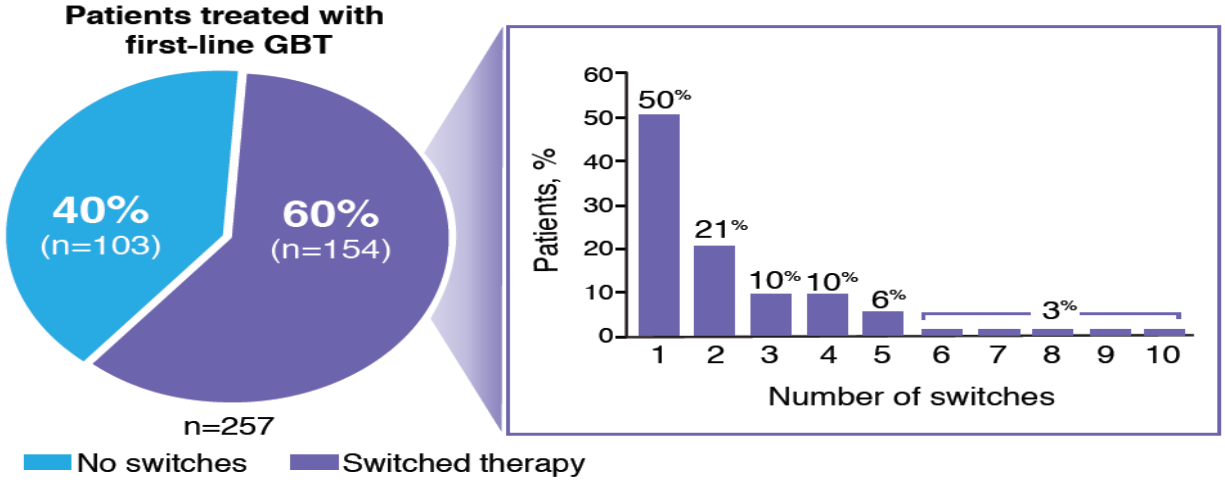
Switches of Therapy

Figure 5. Switches of Therapy Among Patients Who Used GBT as First–line Therapy



- 26% (27/103) of patients did not switch therapy and went off for good within 6 months

Additional Data from ALIS (Amikacin Liposome Inhalation Suspension) Phase 3

Previously Disclosed INS-212 Topline Results from September 2017		
	Patients in INS-212 (n=336)	**Percent Achieving Sputum Culture Conversion by Month 6**
ALIS + GBT	224	29% (n=65/224)
GBT only	112	9% (n=10/112)

Impact of treating patients with ALIS + GBT		
	Number of Patients Completing Six Months of Treatment in INS-312 as of December 2017	**Percent Achieving Sputum Culture Conversion by Month 6 in INS-312**
Patients who received GBT only in INS-212 and crossed over to receiving six months of treatment with ALIS + GBT (n=90)	67	28.4% (19/67)
Patients who received ALIS + GBT in INS-212 and continued treatment in INS-312, for a combined total of 14 months of ALIS + GBT treatment in both studies (n=73)	57	12.3% (7/57)

Durability of Culture Conversion 3 Months After all Treatment is Stopped		
	Evaluable Number of Patients as of December 2017 (At Least Three Months Post-Treatment)	**Percent with Durable Sputum Culture Conversion Three Months After Completion of Treatment**
Converters in the ALIS + GBT arm (n=65)	46	60.9% (28/46)
Converters in the GBT only arm (n=10)	7	0.0% (0/7)

Tuberculosis: mother of thoracic surgery then and now, past and prospectives: a review

Tamas F. Molnar[1,2]

societies' immunity is weakening. Thoracic surgery has a significant share in the fight against tuberculosis, when drugs and/or society fail. Palliative and radical adjuvant surgery multiplies the chance of cure in those cases, where not much hope is left. The jury is still out in a series of questions, but it is obvious, that surgery is only an option and not a panacea where medicines and their providers fail. Deeper understanding of our past and present failures with tuberculosis and its surgery might contribute to new concepts in coping with lung cancer as well.

J Thorac Dis 2018

Surgical Treatment of Complications of Pulmonary Tuberculosis, including Drug-Resistant Tuberculosis

Rajhmun Madansein [a,b,c,*], Shreemanta Parida [d], Nesri Padayatchi [c,e], Nalini Singh [b,c], Iqbal Master [b,c], Kantharuben Naidu [b,c], Alimuddin Zumla [f], Markus Maeurer [d,g]

The classic indications for lung resection in TB are recurrent chest infections, recurrent minor hemoptysis, massive hemoptysis, DR-TB, any complication of TB (*empyema thoracis*, broncho-pleural fistula) persistent sputum positivity with irreversible pulmonary destruction; cavitation and/or bronchiectasis and suspicion of malignancy.[8] Surgery usually entails either lobectomy, bilobectomy, pneumonectomy or staged lobectomies for localized bilateral disease. Wedge or segmental resections are usually avoided due to the increased risk of a bronchopleural fistula. Occasionally, it is performed in the case of upper lobar disease warranting upper lobectomy as well as apical lower segmental disease, given that the basal segments are adequate to fill the pleural space.

Observational studies with surgical interventions have shown a high treatment success rate when used as adjunctive therapy in M/XDR-TB patients, however there has been lack of randomized controlled trials of surgical resections. In many cases of complicated M/XDR-TB with localized lesions and tissue destruction along with failure to become culture negative, adjunctive surgical therapy may play a major role in improving clinical outcome. Collaboration and synergy between clinicians (from various disciplines) and basic scientists is critical for making tangible progress toward achieving control of the TB epidemic.

SECTION 16: WHAT IS THE ROLE OF SURGERY IN THE TREATMENT OF NTM-PULMONARY DISEASE?

Recommendations

- The role of lung resection surgery in the management of NTM-pulmonary disease should be considered at the time of diagnosis and revisited in individuals who develop refractory disease. (Grade D)
- Lung resection surgery for NTM-pulmonary disease may be indicated in individuals with localised areas of severe disease. (Grade D)
- Lung resection surgery for NTM-pulmonary disease should only be performed following expert multidisciplinary assessment in a centre experienced in managing individuals with NTM-pulmonary disease. (Grade D)
- Individuals with NTM-pulmonary disease should be established on antibiotic treatment prior to lung resection surgery and should continue treatment for 12 months after culture conversion. (Grade D).
- Following resection of a solitary NTM nodule in an individual with no other features of NTM-pulmonary disease, antibiotic treatment is not usually required. (Grade D)

Evidence statements

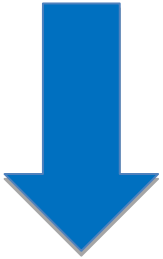
Lung resection surgery in selected individuals with NTM-pulmonary disease can result in a high sputum conversion rate and a low relapse rate. (Evidence Level 3)

Lung resection surgery for NTM-pulmonary disease can be associated with significant morbidity and the complication rate is higher with more extensive resection/pneumonectomy. (Evidence level 3)

Increased operator/centre expertise in performing lung resection surgery for NTM-pulmonary disease is associated with reduced postoperative morbidity and mortality. (Evidence Level 3)

CONCLUSIONI

DIVERGENZE PARALLELE TB/NTM



CONVERGENZA STRATEGICA

- **TB** : CONTROLLO MALATTIA/CENTRI ECCELLENZA MDR
- **NTM** : GRUPPI MULTIDISCIPLINARI

TEAMWORK
AIG
AIG
AIG
AIG