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**境外学者发表的结核病英文文章摘要**

**（79篇）**

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**((tuberculosis[Title/Abstract]) AND (English[Language])) NOT (China[Affiliation])**

**1. J Immunol. 2021 Sep 3:ji2001044. doi: 10.4049/jimmunol.2001044. Online ahead of**

**print.**

A Pulmonary Lactobacillus murinus Strain Induces Th17 and RORγt(+) Regulatory T

Cells and Reduces Lung Inflammation in Tuberculosis.

Bernard-Raichon L(1), Colom A(2), Monard SC(2), Namouchi A(3), Cescato M(2),

Garnier H(2), Leon-Icaza SA(2), Métais A(2), Dumas A(2), Corral D(2),

Ghebrendrias N(2), Guilloton P(2), Vérollet C(2), Hudrisier D(2), Remot A(4),

Langella P(4), Thomas M(4), Cougoule C(2), Neyrolles O(2), Lugo-Villarino G(1).

Author information:

(1)Institut de Pharmacologie et Biologie Structurale, Université de Toulouse,

CNRS, UPS, Toulouse, France; lugo@ipbs.fr lucie.bernard03@gmail.com.

(2)Institut de Pharmacologie et Biologie Structurale, Université de Toulouse,

CNRS, UPS, Toulouse, France.

(3)Centre for Integrative Genetics, Norwegian University of Life Sciences, As,

Norway; and.

(4)Micalis Institute, INRAE, AgroParisTech, Université Paris-Saclay,

Jouy-en-Josas, France.

The lungs harbor multiple resident microbial communities, otherwise known as the

microbiota. There is an emerging interest in deciphering whether the pulmonary

microbiota modulate local immunity, and whether this knowledge could shed light

on mechanisms operating in the response to respiratory pathogens. In this study,

we investigate the capacity of a pulmonary Lactobacillus strain to modulate the

lung T cell compartment and assess its prophylactic potential upon infection

with Mycobacterium tuberculosis, the etiological agent of tuberculosis. In naive

mice, we report that a Lactobacillus murinus (Lagilactobacillus murinus) strain

(CNCM I-5314) increases the presence of lung Th17 cells and of a regulatory T

cell (Treg) subset known as RORγt+ Tregs. In particular, intranasal but not

intragastric administration of CNCM I-5314 increases the expansion of these lung

leukocytes, suggesting a local rather than systemic effect. Resident Th17 and

RORγt+ Tregs display an immunosuppressive phenotype that is accentuated by CNCM

I-5314. Despite the well-known ability of M. tuberculosis to modulate lung

immunity, the immunomodulatory effect by CNCM I-5314 is dominant, as Th17 and

RORγt+ Tregs are still highly increased in the lung at 42-d postinfection.

Importantly, CNCM I-5314 administration in M. tuberculosis-infected mice results

in reduction of pulmonary inflammation, without increasing M. tuberculosis

burden. Collectively, our findings provide evidence for an immunomodulatory

capacity of CNCM I-5314 at steady state and in a model of chronic inflammation

in which it can display a protective role, suggesting that L. murinus strains

found in the lung may shape local T cells in mice and, perhaps, in humans.

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PMID: 34479945

**2. BMJ Case Rep. 2021 Sep 3;14(9):e242907. doi: 10.1136/bcr-2021-242907.**

Oesophagomediastinal fistula: a rare complication of tuberculosis.

Nedkov Gambin M(1), Vella SM(2), Vella C(2), Schembri J(2).

Author information:

(1)Department of Medicine, Mater Dei Hospital, Msida, Malta mebemau@gmail.com.

(2)Department of Medicine, Mater Dei Hospital, Msida, Malta.

We report a case of a woman from Thailand, living in Malta, who was diagnosed

with concomitant tuberculosis (TB) and HIV with depleted CD4 count. Her case was

further complicated by the formation of a fistula between the mediastinal lymph

nodes and the oesophagus, an unusual finding but for which she had many risk

factors. The diagnosis was suspected on CT scan of the thorax and confirmed via

upper gastrointestinal endoscopy. Following the commencement of both anti-TB and

antiretroviral therapy, she suffered a lapse of immune reconstitution

inflammatory syndrome but with aggressive medical management eventually made a

full recovery without the need for surgical intervention.

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**3. Vet Immunol Immunopathol. 2021 Aug 28;240:110320. doi:**

**10.1016/j.vetimm.2021.110320. Online ahead of print.**

Novel polyprotein antigens designed for improved serodiagnosis of bovine

tuberculosis.

Lyashchenko KP(1), Sikar-Gang A(2), Sridhara AA(2), Johnathan-Lee A(2), Elahi

R(2), Lambotte P(2), Esfandiari J(2), Duthie M(3), Reed SG(3), Jones G(4),

Vordermeier HM(4), Thacker TC(5), Palmer MV(5), Waters WR(5).

Author information:

(1)Chembio Diagnostic Systems, Inc., 3661 Horseblock Road, Medford, NY, 11763,

USA. Electronic address: klyashchenko@chembio.com.

(2)Chembio Diagnostic Systems, Inc., 3661 Horseblock Road, Medford, NY, 11763,

USA.

(3)Infectious Disease Research Institute, Seattle, WA, USA.

(4)Tuberculosis Research Group, Animal and Plant Health Agency, Addlestone, UK.

(5)National Animal Disease Center, Agricultural Research Service, United States

Department of Agriculture, 1920 Dayton Avenue, Ames, IA, 50010, USA.

Recent studies have demonstrated potential for serologic assays to improve

surveillance and control programs for bovine tuberculosis. Due to the

animal-to-animal variation of the individual antibody repertoires observed in

bovine tuberculosis, it has been suggested that serodiagnostic sensitivity can

be maximized by use of multi-antigen cocktails or genetically engineered

polyproteins expressing immunodominant B-cell epitopes. In the present study, we

designed three novel multiepitope polyproteins named BID109, TB1f, and TB2f,

with each construct representing a unique combination of four full-length

peptides of Mycobacterium bovis predominantly recognized in bovine tuberculosis.

Functional performance of the fusion antigens was evaluated using multi-antigen

print immunoassay (MAPIA) and Dual Path Platform (DPP) technology with panels of

monoclonal and polyclonal antibodies generated against individual proteins

included in the fusion constructs as well as with serum samples from M.

bovis-infected and non-infected cattle, American bison, and domestic pigs. It

was shown that epitopes of each individual protein were expressed in the fusion

antigens and accessible for efficient binding by the respective antibodies. The

three fusion antigens demonstrated stronger immunoreactivity in MAPIA than that

of single protein antigens. Evaluation of the fusion antigens in DPP assay using

serum samples from 125 M. bovis-infected and 57 non-infected cattle showed the

best accuracy (∼84 %) for TB2f antigen composed of MPB70, MPB83, CFP10, and

Rv2650c proteins. Thus, the study results suggest a potential for the

multiepitope polyproteins to improve diagnostic sensitivity of serologic assays

for bovine tuberculosis.

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PMID: 34479106

**4. Ann Am Thorac Soc. 2021 Sep 3. doi: 10.1513/AnnalsATS.202010-1240OC. Online**

**ahead of print.**

Pulmonary Tuberculosis and the Incidence of Lung Cancer among Patients with

Chronic Obstructive Pulmonary Disease.

Park HY(1), Kang D(2), Shin SH(3), Choi H(4), Jang SH(5), Lee CH(6), Kim H(7),

Kwon OJ(8), Rhee CK(9), Cho J(10).

Author information:

(1)Samsung Medical Center, , Division of Pulmonary and Critical Care Medicine,

Department of Medicine, Seoul, Korea (the Republic of).

(2)SAIHST, Sungkyunkwan University, Departments of Health Sciences and

Technology and Clinical Research Design and Evaluation, Seoul, Korea (the

Republic of).

(3)Samsung Medical Center, 36626, Division of Pulmonary and Critical Care

Medicine, Department of Medicine, Gangnam-gu, Seoul, Korea (the Republic of).

(4)Hallym University College of Medicine, 96664, Chuncheon, Gangwon, Korea (the

Republic of).

(5)Division of Pulmonary, Allergy and Critical Care Medicine, Hallym University

Sacred Heart Hospital, Hallym University College of Medicine, Seoul, Korea (the

Republic of).

(6)Seoul National University College of Medicine, 37990, Seoul, Korea (the

Republic of).

(7)Sungkyunkwan University School of Medicine, Samsung Medical Center,

Department oh Medicine, Division of Respiratory and Critical Medicine, Seoul,

Korea (the Republic of).

(8)Samsung Medical Center, Division of Pulmonary and Critical Care Medicine,

Department of Medicine, Seoul, Korea (the Republic of).

(9)Catholic university of Korea, Internal medicine, Seoul, Korea (the Republic

of).

(10)SAIHST, Department of Clinical Research Design and Evaluation, Seoul, Korea

(the Republic of); jcho@skku.edu.

**RATIONALE:** While the history of pulmonary tuberculosis (PTB) is a risk factor

for developing both chronic obstructive pulmonary disease (COPD) and lung

cancer, it remains unclear whether the history of PTB affects lung cancer

development in COPD patients.

**OBJECTIVES:** To investigate whether a history of PTB is associated with an

increased risk of lung cancer development in a population with COPD.

**METHODS**: This cohort study included a nationwide representative sample of 13,165

Korean men and women with COPD, aged between 50-84 years. In addition, to assess

whether the relationship between PTB and lung cancer risk differs between

participants with and without COPD, a matched cohort without COPD was included.

Participants were matched 1:3 for age, sex, smoking history, and PTB status

based on the index health screening exam of corresponding participants with

COPD. The two cohorts were followed up for 13 years (January 1st, 2003, to

December 31st, 2015). PTB was diagnosed based on the results of chest

radiography, and incident lung cancer was identified from hospitalization and

outpatient visit claims (International Classification of Diseases, Tenth

Revision diagnosis code C33 or C34).

**RESULTS:** During 370,617 person-years (PY) of follow-up (median follow-up, 7.7

years), in the COPD group, we observed 430 incident cases of lung cancer in

participants without a history of PTB (incidence rate 524 per 100,000 PY) and

148 cases in those with a history of PTB (incidence rate 931 per 100,000 PY).

Compared to participants without a PTB history, the fully adjusted

subdistribution hazard ratio (95% confidence interval) for lung cancer in those

with a history of PTB was 1.24 (1.03, 1.50). The association of PTB history and

lung cancer development was more evident in never-smokers with COPD. In

contrast, among participants without COPD, the corresponding hazard ratio (95%

confidence interval) was 0.98 (0.78, 1.22). There was no interaction between

PTB, smoking status, and COPD.

**CONCLUSIONS:** The history of PTB was associated with an increased risk of

developing lung cancer among COPD patients in our country with an intermediate

TB burden. COPD patients with a history of PTB, particularly the never-smokers,

might benefit from periodical screening or assessment for lung cancer

development.

DOI: 10.1513/AnnalsATS.202010-1240OC

PMID: 34478360

**5. Soc Work Public Health. 2021 Sep 3:1-11. doi: 10.1080/19371918.2021.1953665.**

**Online ahead of print.**

Voices of Those Who Bear the Brunt - Experiences of Programme Personnel

Concerning Private Sector Tuberculosis Notifications in Bengaluru City, India.

Meundi AD(1)(2), Erasmus V(2), Nagaraja SB(3), Richardus JH(2).

Author information:

(1)Department of Community Medicine, Bowring and Lady Curzon Medical College and

Research Institute, Bangalore, India.

(2)Department of Public Health, Erasmus MC, University Medical Center,

Rotterdam, The Netherlands.

(3)Department of Community Medicine, ESIC Medical College and PGIMSR, Bangalore,

India.

This study aims to assess private and public sector contributions to

Tuberculosis (TB) notification in Bengaluru city (2011 to 2016) and identify

challenges of program personnel in their interaction with private practitioners

and procedural barriers for TB notification from the private sector as perceived

by them. A mixed methods study was carried out in Bengaluru city, India with TB

notification data obtained from TB Units in addition to in-depth interviews with

key program implementers. Results showed the contribution of private

practitioners to TB notification to be about 20%. Barriers and challenges were:

the private practitioners' hesitancy to refer the patients to public sector due

to their fear of losing patients and dishonoring of diagnosis from private

practitioners, lack of awareness about TB notification, lack of legal punitive

measures and constant glitches on the notification website. These need to be

resolved on priority to achieve the national target of TB elimination by 2025.

DOI: 10.1080/19371918.2021.1953665

PMID: 34478354

**6. ACS Infect Dis. 2021 Sep 3. doi: 10.1021/acsinfecdis.1c00283. Online ahead of**

**print.**

Total Synthesis of Tetrahydrolipstatin, Its Derivatives, and Evaluation of Their

Ability to Potentiate Multiple Antibiotic Classes against Mycobacterium Species.

Khan SS(1), Sudasinghe TD(2), Landgraf AD(1), Ronning DR(2), Sucheck SJ(1).

Author information:

(1)Department of Chemistry & Biochemistry, University of Toledo, Toledo, Ohio

43606, United States.

(2)Department of Pharmaceutical Sciences, University of Nebraska Medical Center,

Omaha, Nebraska 68198, United States.

Tetrahydrolipstatin (THL, 1a) has been shown to inhibit both mammalian and

bacterial α/β hydrolases. In the case of bacterial systems, THL is a known

inhibitor of several Mycobacterium tuberculosis hydrolases involved in

mycomembrane biosynthesis. Herein we report a highly efficient eight-step

asymmetric synthesis of THL using a route that allows modification of the THL

α-chain substituent to afford compounds 1a through 1e. The key transformation in

the synthesis was use of a (TPP)CrCl/Co2(CO)8-catalyzed regioselective and

stereospecific carbonylation on an advanced epoxide intermediate to yield a

trans-β-lactone. These compounds are modest inhibitors of Ag85A and Ag85C, two

α/β hydrolases of M. tuberculosis involved in the biosynthesis of the

mycomembrane. Among these compounds, 10d showed the highest inhibitory effect on

Ag85A (34 ± 22 μM) and Ag85C (66 ± 8 μM), and its X-ray structure was solved in

complex with Ag85C to 2.5 Å resolution. In contrast, compound 1e exhibited the

best-in-class MICs of 50 μM (25 μg/mL) and 16 μM (8.4 μg/mL) against M.

smegmatis and M. tuberculosis H37Ra, respectively, using a microtiter assay

plate. Combination of 1e with 13 well-established antibiotics synergistically

enhanced the potency of few of these antibiotics in M. smegmatis and M.

tuberculosis H37Ra. Compound 1e applied at concentrations 4-fold lower than its

MIC enhanced the MIC of the synergistic antibiotic by 2-256-fold. In addition to

observing synergy with first-line drugs, rifamycin and isoniazid, the MIC of

vancomycin against M. tuberculosis H37Ra was 65 μg/mL; however, the MIC was

lowered to 0.25 μg/mL in the presence of 2.1 μg/mL 1e demonstrating the

potential of targeting mycobacterial hydrolases involved in mycomembrane and

peptidoglycan biosynthesis.

DOI: 10.1021/acsinfecdis.1c00283

PMID: 34478259

**7. Curr Top Med Chem. 2021 Sep 2. doi: 10.2174/1568026621999210902124524. Online**

**ahead of print.**

The medicinal chemistry of 3-nitro-1,2,4-triazoles: focus on infectious

diseases.

França RRF(1), Menozzi CAC(1), Castelo-Branco FS(2), Hoelz LVB(2), Boechat N(2).

Author information:

(1)Programa de Pós-Graduação em Farmacologia e Química Medicinal - PPGFQM-

Instituto de Ciências Biomédicas, Universidade Federal do Rio de Janeiro, Bloco

J, Ilha do Fundão, 21941-902, Rio de Janeiro - RJ. Brazil.

(2)Laboratório de Síntese de Fármacos - LASFAR, Instituto de Tecnologia em

Fármacos, Fundação Oswaldo Cruz, Farmanguinhos - Fiocruz, Manguinhos, 21041-250

Rio de Janeiro - RJ. Brazil.

Infectious diseases are among the leading causes of death worldwide, especially

in developing countries. The historical lack of interest of the pharmaceutical

industry in developing new drugs against many of these diseases, such as

tuberculosis, leishmaniasis, Chagas disease, sleeping sickness, and fungal

infections, has left millions of individuals dependent on old treatments that

are often ineffective and present different adverse effects. In this sense, new

substances against these diseases must be identified. A class of substances that

has stood out in the search for new drugs against these diseases is azole

derivatives. Within this class, the 3-nitro-1,2,4-triazole nucleus has attracted

increasing interest due to its potential, specifically when compared to the

1,2,4-triazole nucleus without the presence of the nitro group, and also in

relation to the 2-nitroimidazole nucleus, showing greater potency and

selectivity against different etiological agents. This is even more relevant

considering that 3-nitro-1,2,4-triazolic substances can promote their activity

through different mechanisms of action, such as the inhibition of ergosterol

biosynthesis and also via activation by the nitroreductase enzyme, which can

avoid the development of cross-resistance. Therefore, in this review, the

medicinal chemistry of nitrotriazoles is discussed through the analysis of their

potential in terms of biological activity against the etiological agents of

several diseases, such as Chagas disease, sleeping sickness and leishmaniasis,

caused by kinetoplastid parasites, tuberculosis, caused by the mycobacteria

Mycobacterium tuberculosis, and against different species of pathogenic fungi.

In addition, aspects related to enzymatic activities, molecular modeling and

organic synthesis of these substances are also addressed.

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PMID: 34477523

**8. Drug Deliv Transl Res. 2021 Sep 3. doi: 10.1007/s13346-021-01055-9. Online ahead**

**of print.**

Appraisal of fluoroquinolone-loaded carubinose-linked hybrid nanoparticles for

glycotargeting to alveolar macrophages.

Maurya P(1), Saklani R(2), Singh S(1), Nisha R(1), Pal RR(1), Mishra N(1), Singh

P(1), Kumar A(2), Chourasia MK(2), Saraf SA(3).

Author information:

(1)Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University

(A Central University, ) Vidya Vihar, Raebareli Road, Lucknow, 226025, India.

(2)Department of Pharmaceutics and Pharmacokinetics, CSIR-Central Drug Research

Institute, Sector 10, Jankipuram Extension, Sitapur Road, Lucknow, 226031,

India.

(3)Department of Pharmaceutical Sciences, Babasaheb Bhimrao Ambedkar University

(A Central University, ) Vidya Vihar, Raebareli Road, Lucknow, 226025, India.

shubhini.saraf@gmail.com.

There is a curious case in Alveolar macrophages (AM), the frontline defence

recruits that contain the spread of all intruding bacteria. In response to

Mycobacterium tuberculosis (M.tb), AM either contain the spread or are modulated

by M.tb to create a region for their replication. The M.tb containing granulomas

so formed are organised structures with confined boundaries. The limited

availability of drugs inside AM aid drug tolerance and poor therapeutic outcomes

in diseases like tuberculosis. The present work proves the glycotargeting

efficiency of levofloxacin (LVF) to AM. The optimised formulation developed

displayed good safety with 2% hemolysis and a viability of 61.14% on J774A.1

cells. The physicochemical characterisations such as Fourier-transform infrared

spectroscopy (FTIR), X-ray diffraction (XRD), differential scanning calorimetry

(DSC) and thermogravimetric analysis (TGA) proved that carubinose linkage was

accomplished and LVF is entrapped inside carubinose-linked hybrid formulation

(CHF) and hybrid formulation (HF) in amorphous form. The transmission electron

microscopy (TEM) images revealed a core-shell structure of HF. The particle size

of 471.5 nm estimated through dynamic light scattering (DLS) is enough to

achieve active and passive targeting to AM. The nanoparticle tracking analysis

(NTA) data revealed that the diluted samples were free from aggregates.

Fluorescence-activated cell sorting (FACS) data exhibited excellent uptake via

CHF (15 times) and HF(3 times) with reference to plain fluorescein

isothiocyanate (FITC). The pharmacokinetic studies revealed that CHF and HF

release the entrapped moiety LVF in a controlled manner over 72 h. The stability

studies indicated that the modified formulation remains stable over 6 months at

5 ± 3℃. Hence, hybrid systems can be efficiently modified via carubinose to

target AM via the parenteral route.

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DOI: 10.1007/s13346-021-01055-9

PMID: 34476764

**9. ERJ Open Res. 2021 Aug 31;7(3):00251-2021. doi: 10.1183/23120541.00251-2021.**

**eCollection 2021 Jul.**

Psychological stress and health-related quality of life among tuberculosis

patients: a prospective cohort study.

Febi AR(1), Manu MK(2), Mohapatra AK(1)(3), Praharaj SK(2), Guddattu V(3).

Author information:

(1)Dept of Respiratory Medicine, Kasturba Medical College, Manipal, Manipal

Academy of Higher Education, Manipal, Karnataka, India.

(2)Dept of Psychiatry, Kasturba Medical College, Manipal, Manipal, Manipal

Academy of Higher Education, Manipal, Karnataka, India.

(3)Dept of Data Science, Prasanna School of Public health, Manipal, Manipal

Academy of Higher Education, Manipal, Karnataka, India.

Economic, social and psychological distress is common in individuals affected by

tuberculosis (TB). However, the magnitude of distress, psychological

interventions and their effect on the treatment outcomes are often

under-evaluated. We examined the level of psychological stress and

health-related quality of life (HRQoL) of such patients and the effect of

antituberculosis therapy on them.  Our prospective cohort study included newly

diagnosed adult pulmonary and extrapulmonary TB patients. Assessment of

psychological stress was done using the seven-item Generalised Anxiety Disorder

questionnaire for anxiety and the nine-item Patient Health Questionnaire for

depression. HRQoL was assessed by using the WHOQOL-BREF questionnaire.  Of the

86 patients studied, 21 (24.4%) had anxiety symptoms at the baseline, which

reduced to 5.8% and 1.2% at 2 months and treatment completion, respectively

(p<0.001). Among the subjects, 18 (20.9%) patients had depression, which reduced

to 7% and 2.3% at 2 months and treatment completion, respectively (p<0.001). All

the mean domain scores of HRQoL were poor at the baseline, which showed

improvement at treatment completion (p<0.001).  Anxiety and depression were

common among TB patients, and there was significant progressive reduction during

and after treatment. TB had remarkable negative impacts on HRQoL, with the

physical domain being the most affected, and all the domain scores showed

significant improvement at treatment completion. Routine screening for

depression and anxiety and timely referral to a psychiatrist are required in TB

patients to improve the outcome of the disease and quality of life.

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PMCID: PMC8405877

PMID: 34476253

**10. Sci Rep. 2021 Sep 2;11(1):17540. doi: 10.1038/s41598-021-97010-2.**

MPT64 antigen detection test improves diagnosis of pediatric extrapulmonary

tuberculosis in Mbeya, Tanzania.

Grønningen E(1)(2), Nanyaro M(3), Sviland L(4)(5), Ngadaya E(3), Muller W(3)(6),

Torres L(3)(6), Mfinanga S(3), Mustafa T(7)(8).

Author information:

(1)Department of Global Public Health and Primary Care, Centre for International

Health, University of Bergen, 5020, Bergen, Norway. erlend.gronningen@uib.no.

(2)Department of Thoracic Medicine, Haukeland University Hospital, 5021, Bergen,

Norway. erlend.gronningen@uib.no.

(3)Muhimbili Medical Research Centre, National Institute for Medical Research,

Dar es Salaam, United Republic of Tanzania.

(4)Department of Clinical Medicine, Faculty of Medicine, University of Bergen,

5020, Bergen, Norway.

(5)Department of Pathology, Haukeland University Hospital, Bergen, Norway.

(6)Mbeya Zonal Referral Hospital, Mbeya, United Republic of Tanzania.

(7)Department of Global Public Health and Primary Care, Centre for International

Health, University of Bergen, 5020, Bergen, Norway.

(8)Department of Thoracic Medicine, Haukeland University Hospital, 5021, Bergen,

Norway.

Pediatric extrapulmonary tuberculosis (EPTB) is a diagnostic challenge. A new

immunochemistry based MPT64 antigen detection test has shown improved

sensitivity compared to current laboratory tests. The aim of this study was to

implement and validate the test performance in a resource limited African

setting. Presumptive pediatric (0-18 y) EPTB patients were prospectively

enrolled at Mbeya Zonal Referral Hospital, and followed to the end of treatment

or until a final diagnosis was reached. Specimens from suspected sites of

infection were subject to routine diagnostics, GeneXpert MTB/RIF assay and the

MPT64 test. The performance of the tests was assessed using mycobacterial

culture as well as a composite reference standard. 30 patients were categorized

as TB cases, 31 as non-TB cases and 2 were uncategorized. In the TB group, the

three most common infections were adenitis (30%), peritonitis (30%) and

meningitis (20%). The sensitivity, specificity, positive predictive value,

negative predictive value and accuracy of the MPT64 test was 92%, 88%, 87%, 92%

and 90%, respectively. Mortality was equally high among TB/non-TB cases (23% vs

21%), and malnutrition was the main comorbidity among TB cases. The MPT64 test

was implementable in the routine diagnostics in a low-resource setting and

improved the diagnosis of pediatric EPTB.

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DOI: 10.1038/s41598-021-97010-2

PMCID: PMC8413277

PMID: 34475471

**11. Nat Commun. 2021 Sep 2;12(1):5236. doi: 10.1038/s41467-021-25537-z.**

The cryo-EM structure of the bd oxidase from M. tuberculosis reveals a unique

structural framework and enables rational drug design to combat TB.

Safarian S(1), Opel-Reading HK(2), Wu D(3), Mehdipour AR(4), Hards K(5), Harold

LK(5), Radloff M(3), Stewart I(6), Welsch S(7), Hummer G(4)(8), Cook GM(5),

Krause KL(2), Michel H(9).

Author information:

(1)Department of Molecular Membrane Biology, Max Planck Institute of Biophysics,

Frankfurt/Main, Germany. schara.safarian@biophys.mpg.de.

(2)Department of Biochemistry, University of Otago, Dunedin, New Zealand.

(3)Department of Molecular Membrane Biology, Max Planck Institute of Biophysics,

Frankfurt/Main, Germany.

(4)Department of Theoretical Biophysics, Max Planck Institute of Biophysics,

Frankfurt/Main, Germany.

(5)Department of Microbiology and Immunology, School of Biomedical Sciences,

University of Otago, Dunedin, New Zealand.

(6)Department of Chemistry, University of Otago, Dunedin, New Zealand.

(7)Central Electron Microscopy Facility, Max Planck Institute of Biophysics,

Frankfurt am Main, Germany.

(8)Institute of Biophysics, Goethe University Frankfurt, Frankfurt/Main,

Germany.

(9)Department of Molecular Membrane Biology, Max Planck Institute of Biophysics,

Frankfurt/Main, Germany. hartmut.michel@biophys.mpg.de.

New drugs are urgently needed to combat the global TB epidemic. Targeting

simultaneously multiple respiratory enzyme complexes of Mycobacterium

tuberculosis is regarded as one of the most effective treatment options to

shorten drug administration regimes, and reduce the opportunity for the

emergence of drug resistance. During infection and proliferation, the cytochrome

bd oxidase plays a crucial role for mycobacterial pathophysiology by maintaining

aerobic respiration at limited oxygen concentrations. Here, we present the

cryo-EM structure of the cytochrome bd oxidase from M. tuberculosis at 2.5 Å. In

conjunction with atomistic molecular dynamics (MD) simulation studies we

discovered a previously unknown MK-9-binding site, as well as a unique disulfide

bond within the Q-loop domain that defines an inactive conformation of the

canonical quinol oxidation site in Actinobacteria. Our detailed insights into

the long-sought atomic framework of the cytochrome bd oxidase from M.

tuberculosis will form the basis for the design of highly specific drugs to act

on this enzyme.

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DOI: 10.1038/s41467-021-25537-z

PMID: 34475399

**12. Acta Chir Belg. 2021 Sep 3:1-19. Online ahead of print.**

Preserving the eponym: Klinkenbergh technique for bronchial stump suturing.

Prisciandaro E(1)(2), Decaluwé H(1)(2), De Leyn P(1)(2), Coosemans W(1)(2),

Nafteux P(1)(2), Van Veer H(1)(2), Depypere L(1)(2), Lerut T(1)(2), Van

Raemdonck D(1)(2), Ceulemans LJ(1)(2).

Author information:

(1)Department of Thoracic Surgery, University Hospitals Leuven, Leuven, Belgium.

(2)Department of Chronic Diseases and Metabolism, Laboratory of Respiratory

Diseases and Thoracic Surgery (BREATHE), KU Leuven, Leuven, Belgium.

The technique for bronchial stump suturing following lung resection which is

currently applied in the Department of Thoracic Surgery at the University

Hospitals Leuven, Belgium owes its name to the Dutch surgeon Dr. Klinkenbergh

(1891-1985).A true pioneer of cardio-thoracic surgery in Europe, Dr.

Klinkenbergh dedicated himself to the surgical treatment of pulmonary

tuberculosis. His work was praised by his peers for his precision and the

reasoning behind every gesture.The Klinkenbergh technique consists in performing

two running sutures which cross each other 'in the same manner as the laces of a

shoe' to close the bronchus, limiting the occurrence of broncho-pleural

fistulas. In our experience with more than 100 patients in the last 5 years

(2016-2020) who underwent open pneumonectomy for benign or malignant disease,

less than 2% developed post-operative broncho-pleural fistulas.

PMID: 34474643

**13. Biomol Concepts. 2021 Sep 2;12(1):117-128. doi: 10.1515/bmc-2021-0013.**

3D host cell and pathogen-based bioassay development for testing

anti-tuberculosis (TB) drug response and modeling immunodeficiency.

Mukundan S(1), Bhatt R(1), Lucas J(1), Tereyek M(1), Chang TL(2), Subbian S(2),

Parekkadan B(3).

Author information:

(1)Department of Biomedical Engineering, Rutgers, The State University of New

Jersey, NJ 08854.

(2)Public Health Research Institute, New Jersey Medical School, Rutgers, The

State University of New Jersey, NJ 07103.

(3)Department of Biomedical Engineering, Rutgers, The State University of New

Jersey, NJ 08854; Department of Medicine, Rutgers Biomedical Health Sciences,

Rutgers, The State University of New Jersey, NJ 08854.

Tuberculosis (TB) is a global health threat that affects 10 million people

worldwide. Human Immunodeficiency Virus (HIV) remains one of the major

contributors to the reactivation of asymptomatic latent tuberculosis (LTBI).

Over the recent years, there has been a significant focus in developing in-vitro

3D models mimicking early events of Mycobacterium tuberculosis (Mtb)

pathogenesis, especially formation of the granuloma. However, these models are

low throughput and require extracellular matrix. In this article, we report the

generation of a matrix-free 3D model, using THP-1 human monocyte/macrophage

cells and mCherry-expressing Mycobacterium bovis BCG (Bacilli Camille Guérin),

henceforth referred as 3D spheroids, to study the host cell-bacterial

interactions. Using mCherry-intensity-based tracking, we monitored the kinetics

of BCG growth in the 3D spheroids. We also demonstrate the application of the 3D

spheroids for testing anti-TB compounds such as isoniazid (INH), rifampicin

(RIF), as well as a host-directed drug, everolimus (EVR) as single and

combinational treatments. We further established a dual infection 3D spheroid

model by coinfecting THP-1 macrophages with BCG mCherry and pseudotype HIV. In

this HIV-TB co-infection model, we found an increase in BCG mCherry growth

within the 3D spheroids infected with HIV pseudotype. The degree of disruption

of the granuloma was proportional to the virus titers used for co-infection. In

summary, this 3D spheroid assay is an useful tool to screen anti-TB response of

potential candidate drugs and can be adopted to model HIV-TB interactions.

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PMID: 34473918

**14. PLoS Pathog. 2021 Sep 2;17(9):e1009888. doi: 10.1371/journal.ppat.1009888.**

**Online ahead of print.**

The opportunistic intracellular bacterial pathogen Rhodococcusequi elicits type

I interferon by engaging cytosolic DNA sensing in macrophages.

Vail KJ(1)(2), da Silveira BP(3), Bell SL(1), Cohen ND(3), Bordin AI(3), Patrick

KL(1), Watson RO(1).

Author information:

(1)Department of Microbial Pathogenesis and Immunology, Texas A&M Health Science

Center, Bryan, Texas, United States of America.

(2)Department of Veterinary Pathology, Texas A&M University, College Station,

Texas, United States of America.

(3)Department of Large Animal Clinical Sciences, Texas A&M University, College

Station, Texas, United States of America.

Rhodococcusequi is a major cause of foal pneumonia and an opportunistic pathogen

in immunocompromised humans. While alveolar macrophages constitute the primary

replicative niche for R. equi, little is known about how intracellularR. equi is

sensed by macrophages. Here, we discovered that that in addition to previously

characterized pro-inflammatory cytokines (e.g., Tnfa, Il6, Il1b), macrophages

infected with R. equi induce a robust type I IFN response, including Ifnband

interferon-stimulated genes (ISGs), similar to the evolutionarily related

pathogen, Mycobacterium tuberculosis. Follow up studies using a combination of

mammalian and bacterial genetics demonstrated that induction of this type I IFN

expression program is largely dependent on the cGAS/STING/TBK1 axis of the

cytosolic DNA sensing pathway, suggesting that R. equi perturbs the phagosomal

membrane and causes DNA release into the cytosol following phagocytosis.

Consistent with this, we found that a population of ~12% of R. equi phagosomes

recruits the galectin-3,-8 and -9 danger receptors. Interestingly, neither

phagosomal damage nor induction of type I IFN require the R. equi's

virulence-associated plasmid. Importantly, R. equi infection of both mice and

foals stimulates ISG expression, in organs (mice) and circulating monocytes

(foals). By demonstrating that R. equi activates cytosolic DNA sensing in

macrophages and elicits type I IFN responses in animal models, our work provides

novel insights into how R. equi engages the innate immune system and furthers

our understanding how this zoonotic pathogen causes inflammation and disease.

DOI: 10.1371/journal.ppat.1009888

PMID: 34473814

**15. PLoS One. 2021 Sep 2;16(9):e0256795. doi: 10.1371/journal.pone.0256795.**

**eCollection 2021.**

Role of informal healthcare providers in tuberculosis care in low- and

middle-income countries: A systematic scoping review.

Thapa P(1), Jayasuriya R(1), Hall JJ(1), Beek K(1), Mukherjee P(2), Gudi N(3),

Narasimhan P(1).

Author information:

(1)School of Population Health, University of New South Wales, Sydney,

Australia.

(2)Liver Foundation, Kolkata, West Bengal, India.

(3)The George Institute for Global Health, New Delhi, India.

Achieving targets set in the End TB Strategy is still a distant goal for many

Low- and Middle-Income Countries (LMICs). The importance of strengthening

public-private partnership by engaging all identified providers in Tuberculosis

(TB) care has long been advocated in global TB policies and strategies. However,

Informal Healthcare Providers (IPs) are not yet prioritised and engaged in

National Tuberculosis Programs (NTPs) globally. There exists a substantial body

of evidence that confirms an important contribution of IPs in TB care. A

systematic understanding of their role is necessary to ascertain their potential

in improving TB care in LMICs. The purpose of this review is to scope the role

of IPs in TB care. The scoping review was guided by a framework developed by the

Joanna Briggs Institute. An electronic search of literature was conducted in

MEDLINE, EMBASE, SCOPUS, Global Health, CINAHL, and Web of Science. Of a total

5234 records identified and retrieved, 92 full-text articles were screened, of

which 13 were included in the final review. An increasing trend was observed in

publication over time, with most published between 2010-2019. In 60% of the

articles, NTPs were mentioned as a collaborator in the study. For detection and

diagnosis, IPs were primarily involved in identifying and referring patients.

Administering DOT (Directly Observed Treatment) to the patient was the major

task assigned to IPs for treatment and support. There is a paucity of evidence

on prevention, as only one study involved IPs to perform this role. Traditional

health providers were the most commonly featured, but there was not much

variation in the role by provider type. All studies reported a positive role of

IPs in improving TB care outcomes. This review demonstrates that IPs can be

successfully engaged in various roles in TB care with appropriate support and

training. Their contribution can support countries to achieve their national and

global targets if prioritized in National TB Programs.

DOI: 10.1371/journal.pone.0256795

PMCID: PMC8412253

PMID: 34473752

**16. J Clin Invest. 2021 Sep 2:148013. doi: 10.1172/JCI148013. Online ahead of print.**

Alveolar macrophages from persons living with HIV show impaired epigenetic

response to Mycobacterium tuberculosis.

Correa-Macedo W(1), Fava VM(2), Orlova M(2), Cassart P(2), Olivenstein R(3),

Sanz J(4), Xu YZ(2), Dumaine A(5), Sindeaux RH(6), Yotova V(6), Pacis A(7),

Girouard J(8), Kalsdorf B(9), Lange C(9), Routy JP(2), Barreiro LB(5), Schurr

E(2).

Author information:

(1)Department of Biochemistry, McGill University, Montréal, Canada.

(2)Program in Infectious Diseases and Global Health, The Research Institute of

the McGill University Health Centre, Montréal, Canada.

(3)Translational Research in Respiratory Diseases Program, The Research

Institute of the McGill University Health Centre, Montréal, Canada.

(4)Institute for Bio-computation and Physics of Complex Systems BIFI, Departme,

University of Zaragoza, Zaragoza, Spain.

(5)Department of Medicine, University of Chicago, Chicago, United States of

America.

(6)Research Centre, CHU Sainte-Justine Hospital, Montréal, Canada.

(7)Canadian Centre for Computational Genomics, McGill University and Genome

Quebec Innovation Center, Montréal, Canada.

(8)Chronic Viral Illnesses Service and Division of Hematology, McGill

University, Montréal, Canada.

(9)Clinical Infectious Diseases, Research Center Borstel, Borstel, Germany.

Persons living with HIV (PLWH) are at increased risk of tuberculosis (TB).

HIV-associated TB is often the result of recent infection with Mycobacterium

tuberculosis (Mtb) followed by rapid progression to disease. Alveolar

macrophages (AM) are the first cells of the innate immune system that engage

Mtb, but how HIV and antiretroviral therapy (ART) impact on the

anti-mycobacterial response of AM is not known. To investigate the impact of HIV

and ART on the transcriptomic and epigenetic response of AM to Mtb, we obtained

AM by bronchoalveolar lavage from 20 PLWH receiving ART, 16 control subjects who

were HIV-free (HC), and 14 subjects who received ART as pre-exposure prophylaxis

(PrEP) to prevent HIV infection. Following in-vitro challenge with Mtb, AM from

each group displayed overlapping but distinct profiles of significantly up- and

down-regulated genes in response to Mtb. Comparatively, AM isolated from both

PLWH and PrEP subjects presented a substantially weaker transcriptional

response. In addition, AM from HC subjects challenged with Mtb responded with

pronounced chromatin accessibility changes while AM obtained from PLWH and PrEP

subjects displayed no significant changes in their chromatin state.

Collectively, these results revealed a stronger adverse effect of ART than HIV

on the epigenetic landscape and transcriptional responsiveness of AM.

DOI: 10.1172/JCI148013

PMID: 34473646

**17. Curr Diabetes Rev. 2021 Sep 2. doi: 10.2174/1573399817666210902144539. Online**

**ahead of print.**

Effect of Vitamin D Supplementation in Type 2 Diabetes Patients with

Tuberculosis: A Systematic Review.

Patel DG(1), Kurian SJ(1), Miraj SS(1), Rashid M(1), Thomas L(1), Rodrigues

GS(2), Banerjee M(3), Khandelwal B(4), Saravu K(5), Rao M(1).

Author information:

(1)Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences,

Manipal Academy of Higher Education, Manipal, Karnataka-576104, India.

(2)Department of Surgery Kasturba Medical College and Hospital, Manipal Academy

of Higher Education, Manipal, Karnataka-576104, India.

(3)Department of Biochemistry All India Institute of Medical Sciences Jodhpur,

Rajasthan-342005, India.

(4)Department of Medicine Sikkim Manipal Institute of Medical Sciences Sikkim

Manipal University, Gangtok, Sikkim-737102, India.

(5)Manipal Center for Infectious Diseases, Prasanna School of Public Health,

Manipal Academy of Higher Education, Manipal, Karnataka-576104, India.

**BACKGROUND:** Diabetes mellitus (DM) and tuberculosis (TB) have been recognized as

re-emerging epidemics, especially in developing countries. Among all the risk

factors, diabetes causes immunosuppression, increasing the risk of active TB

three times. Vitamin D has been found as a link between DM-TB co-morbidity.

**OBJECTIVE:** Vitamin D affects the immune response, suppresses Mycobacterium

tuberculosis (Mtb) growth, and affects insulin secretion. The present systematic

review determines the effect of vitamin D supplementation on clinical and

therapeutic outcomes of DM-TB patients.

**METHOD:** A comprehensive literature search was carried out in PubMed, Cochrane,

Web of Science, and Scopus database to determine eligible studies from inception

to January 2021. Out of 639 articles retrieved, three randomized controlled

trials (RCTs) were included in the systematic review.

**RESULT:** The effect of vitamin D3 or oral cholecalciferol supplementation was

assessed on outcomes such as duration to sputum smear conversion, TB scores

improvement, change in glycemic parameters including HbA1c, FBS, and PLBS, and

laboratory parameters such as Hb, ESR, and CRP. Duration of sputum smear

conversion was decreased by two weeks in the vitamin D3 supplemented group in

two studies. TB score improvement and changes in glycemic parameters were

inclined towards supplemented group; however, they were not significant.

**CONCLUSION:** The overall effect of vitamin D3 supplementation on TB patients with

DM was not significant. Further studies are required in the future examining the

effect of supplementation on outcomes in this population.

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epub@benthamscience.net.

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PMID: 34473618

**18. Biochemistry. 2021 Sep 2. doi: 10.1021/acs.biochem.1c00371. Online ahead of**

**print.**

Effect of Sequence on the Interactions of Divalent Cations with M-Box

Riboswitches from Mycobacterium tuberculosis and Bacillus subtilis.

Bahoua B, Sevdalis SE, Soto AM.

RNA is highly negatively charged and often acquires complex structures that

require the presence of divalent cations. Subtle changes in conformation

resulting from changes in sequence can affect the way ions associate with RNA.

Riboswitches are RNA molecules that are involved in the control of gene

expression in bacteria and are excellent systems for testing the effects of

sequence variations on the conformation of RNA because they contain a highly

conserved binding pocket but present sequence variability among different

organisms. In this work, we have compared the aptamer domain of a proposed M-box

riboswitch from Mycobacterium tuberculosis with the aptamer domain of a

validated M-box riboswitch from Bacillus subtilis. We have in vitro transcribed

and purified wild-type (WT) M-box riboswitches from M. tuberculosis and B.

subtilis as well as a variety of mutated aptamers in which regions from one

riboswitch have been replaced with regions from the other riboswitch. We have

used ultraviolet unfolding experiments and circular dichroism to characterize

the interactions of WT and related M-box riboswitches with divalent cations. Our

results show that M-box from M. tuberculosis associates with Mg2+ and Sr2+ in a

similar fashion while M-box from B. subtilis discriminates between these two

ions and appears to associate better with Mg2+. Our overall results show that

M-box from M. tuberculosis interacts differently with cations than M-box from B.

subtilis and suggest conformational differences between these two riboswitches.

DOI: 10.1021/acs.biochem.1c00371

PMID: 34472844

**19. Sci Rep. 2021 Sep 1;11(1):15523. doi: 10.1038/s41598-021-93967-2.**

Deep learning for distinguishing normal versus abnormal chest radiographs and

generalization to two unseen diseases tuberculosis and COVID-19.

Nabulsi Z(1), Sellergren A(#)(1), Jamshy S(#)(1), Lau C(2), Santos E(1), Kiraly

AP(1), Ye W(1), Yang J(1), Pilgrim R(1), Kazemzadeh S(1), Yu J(1), Kalidindi

SR(3), Etemadi M(4), Garcia-Vicente F(4), Melnick D(4), Corrado GS(1), Peng

L(1), Eswaran K(1), Tse D(5), Beladia N(1), Liu Y(1), Chen PC(6), Shetty S(7).

Author information:

(1)Google Health, Google, Palo Alto, USA.

(2)Google Health Via Advanced Clinical, Deerfield, USA.

(3)Apollo Radiology International, Hyderabad, India.

(4)Northwestern Medicine, Chicago, IL, USA.

(5)Google Health, Google, Palo Alto, USA. tsed@google.com.

(6)Google Health, Google, Palo Alto, USA. cameronchen@google.com.

(7)Google Health, Google, Palo Alto, USA. sshetty@google.com.

(#)Contributed equally

Chest radiography (CXR) is the most widely-used thoracic clinical imaging

modality and is crucial for guiding the management of cardiothoracic conditions.

The detection of specific CXR findings has been the main focus of several

artificial intelligence (AI) systems. However, the wide range of possible CXR

abnormalities makes it impractical to detect every possible condition by

building multiple separate systems, each of which detects one or more

pre-specified conditions. In this work, we developed and evaluated an AI system

to classify CXRs as normal or abnormal. For training and tuning the system, we

used a de-identified dataset of 248,445 patients from a multi-city hospital

network in India. To assess generalizability, we evaluated our system using 6

international datasets from India, China, and the United States. Of these

datasets, 4 focused on diseases that the AI was not trained to detect: 2

datasets with tuberculosis and 2 datasets with coronavirus disease 2019. Our

results suggest that the AI system trained using a large dataset containing a

diverse array of CXR abnormalities generalizes to new patient populations and

unseen diseases. In a simulated workflow where the AI system prioritized

abnormal cases, the turnaround time for abnormal cases reduced by 7-28%. These

results represent an important step towards evaluating whether AI can be safely

used to flag cases in a general setting where previously unseen abnormalities

exist. Lastly, to facilitate the continued development of AI models for CXR, we

release our collected labels for the publicly available dataset.

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DOI: 10.1038/s41598-021-93967-2

PMCID: PMC8410908

PMID: 34471144

**20. Neoreviews. 2021 Sep;22(9):e600-e605. doi: 10.1542/neo.22-9-e600.**

Congenital and Perinatal Tuberculosis.

Shao Y(1), Hageman JR(2), Shulman ST(3).

Author information:

(1)Department of Pediatrics and.

(2)Section of Neonatology, Comer Children's Hospital, University of Chicago

Medical Center, Chicago, IL.

(3)Division of Pediatric Infectious Disease, Ann & Robert H. Lurie Children's

Hospital of Chicago, Northwestern Medical Center, Chicago, IL.

This review discusses the recent literature (2006-2020) about the epidemiology,

clinical presentation, diagnosis, and management of infants with congenital or

perinatal tuberculosis (TB). While the incidence of childhood TB is declining in

the United States and worldwide, many case reports describe how clinical

suspicion for neonatal TB is raised only if an ill-appearing neonate does not

improve with broad-spectrum antibiotics. Furthermore, the delay in initiating

appropriate anti-TB therapy often results in the need for significant

cardiopulmonary support and/or an increase in mortality. This review summarizes

important clinical indications in the maternal and newborn history, the

evaluation of an infant with possible TB exposure, and step-by-step

recommendations for the treatment and follow-up of infants with TB.

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DOI: 10.1542/neo.22-9-e600

PMID: 34470761

**21. J Occup Med Toxicol. 2021 Sep 1;16(1):38. doi: 10.1186/s12995-021-00326-y.**

Prevalence and risk factors for latent tuberculosis in polish healthcare

workers: the comparison of tuberculin skin test and interferon-gamma release

assay (IGRA) performance.

Szturmowicz M(1), Broniarek-Samson B(2), Demkow U(3).

Author information:

(1)1st Department of Lung Diseases, National Tuberculosis and Lung Diseases

Research Institute, Warsaw, Poland.

(2)Department of Laboratory Diagnostics, Institute of Mother and Child, Warsaw,

Poland.

(3)Department of Laboratory Diagnostics and Clinical Immunology of Developmental

Age, Medical University of Warsaw, Warsaw, Poland. urszula.demkow@uckwum.pl.

**BACKGROUND:** Tuberculosis (TB) is still one of the most common infectious

diseases worldwide. Health care workers (HCW) are at particular risk of the

disease due to their constant exposure to TB patients or their specimens,

nevertheless no specific surveillance is widely recommended in this group of

professionals. Both, tuberculin skin test (TST) and

interferon-gamma-release-assays (IGRAs) are widely applied to detect latent

tuberculosis infection (LTBI). The aim of the present study was to evaluate the

prevalence and risks of LTBI in the population of Polish HCW, to identify

factors associated with LTBI, as well as to determine the rate of the

discordance between the results of the two applied tests in relation to various

factors in a TB endemic setting. The study participants were recruited from

several health care facilities (hospitals and outpatients clinics) all over the

country. Laboratory personnel included 156 persons from both TB and non-TB

laboratories (118 clinical pathologists, 38 laboratory technicians), 31 medical

doctors, 29 nurses (from both TB and non-TB wards and from family practices), 6

other medical employees (patients assistants). Out of examined group 88 (40%)

declared constant (everyday) occupational contact with TB patients and/or

contagious biologic materials, 134 (60%) reported sporadic (incidental) contact

(few times a year). Administrative HCWs who were not in direct contact with

patients were not included in the study group.

**MATERIAL AND METHODS:** LTBI status was prospectively evaluated in 222 HCW, 204

females, 18 males, aged 40.8 ± 9 years, with tuberculin skin test (TST) and

interferon gamma release assay (QuantiFERON-TB-Gold in Tube - QFT GIT).

**RESULTS:** TST ≥ 10 mm was found in 58% of HCW, QFT GIT ≥ 0.35 IU/ml in 23%.

Nevertheless the relative number of positive QFT GIT in HCW above 45 years of

age exceeded those obtained in general population (prevalence of positive QTF

test in polish adult population is around 23%). The risk of obtaining positive

QFT GIT was significantly increased in the participants older than 44 years

(OR = 4.95, 95%CI:2.375-10.193), in those employed > 10 years (OR = 2.726,

95%CI:1.126-6.599), and in those who reported the direct contact with

tuberculous patients or infected biological materials (OR = 8.135,

95%CI:1.297-51.016). The concordance between TST and IGRA was poor (kappa 0.23),

especially in younger participants, possibly due to BCG vaccination in

childhood.

**CONCLUSION:** The increased risk of LTBI in Polish HCW was related to age,

duration of employment and contact with infectious patients or their biological

specimens. TB infection control measures in health care facilities in Poland are

still insufficient. It is crucial to increase awareness about the importance of

detecting and treating LTBI of HCW.

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DOI: 10.1186/s12995-021-00326-y

PMID: 34470622

**22. J Clin Microbiol. 2021 Sep 1:JCM0131621. doi: 10.1128/JCM.01316-21. Online ahead**

**of print.**

Xpert MTB/RIF Ultra is highly sensitive for the diagnosis of tuberculosis

lymphadenitis in an HIV-endemic setting.

Minnies S(1), Reeve BWP(1), Rockman L(1), Nyawo G(1), Naidoo CC(1), Kitchin

N(2), Rautenbach C(3)(4), Wright CA(5), Whitelaw A(3)(4), Schubert P(4)(5),

Warren RM(1), Theron G(1).

Author information:

(1)DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, South

African Medical Research Council Centre for Tuberculosis Research, Division of

Molecular Biology and Human Genetics, Faculty of Medicine and Health Sciences,

Stellenbosch University, South Africa.

(2)Department of Psychiatry, Faculty of Medicine and Health Sciences,

Stellenbosch University, South Africa.

(3)Division of Medical Microbiology, Faculty of Medicine and Health Sciences,

Stellenbosch University, South Africa.

(4)National Health Laboratory Services, Cape Town, South Africa.

(5)Division of Anatomical Pathology, Faculty of Medicine and Health Sciences,

Stellenbosch University, South Africa.

**Background**: Tuberculosis lymphadenitis (TBL) is the most common extrapulmonary

TB (EPTB) manifestation. Xpert MTB/RIF Ultra (Ultra) is a World Health

Organization-endorsed diagnostic test, but performance data for TBL, including

on non-invasive specimens, are limited. **Methods:** Fine needle aspiration biopsies

(FNABs) from outpatients (≥18 years) with presumptive TBL (n=135) underwent: 1)

routine Xpert (later Ultra once programmatically available), 2) a MGIT 960

culture (if Xpert- or Ultra-negative, or rifampicin-resistant), and 3) study

Ultra. Concentrated paired urine underwent Ultra. Primary analyses used a

microbiological reference standard (MRS). **Results:** In a head-to-head comparison

(n=92) of FNAB study Ultra and Xpert, Ultra had increased sensitivity [91% (95%

confidence interval 79, 98) vs. 72% (57, 84); p=0.016] and decreased specificity

[76% (61, 87) vs. 93% (82, 99); p=0.020], and detected patients not on

treatment. HIV nor alternative reference standards affected sensitivity and

specificity. In patients with both routine and study Ultras, the latter detected

more cases [+20% (0, 42); p=0.034] and, further indicative of potential

laboratory-based room-for-improvement (e.g., specimen processing optimisation),

false-negative study Ultras were more inhibited than true-positives. Study Ultra

false-positives had less mycobacterial DNA than true-positives [trace-positive

proportions 59% (13/22) vs. 12% (5/51); p<0.001]. "Trace" exclusion or

recategorization removed potential benefits offered over Xpert. Urine Ultra had

low sensitivity [18% (7, 35)]. **Conclusions:** Ultra on FNABs is highly sensitive

and detects more TBL than Xpert. Patients with FNAB Ultra-positive "trace"

results, most of whom will be culture-negative, may require additional clinical

investigation. Urine Ultra could reduce the number of patients needing invasive

sampling.

DOI: 10.1128/JCM.01316-21

PMID: 34469182

**23. Mol Divers. 2021 Sep 1. doi: 10.1007/s11030-021-10296-2. Online ahead of print.**

Drug repositioning for anti-tuberculosis drugs: an in silico polypharmacology

approach.

Madugula SS(1)(2), Nagamani S(3), Jamir E(2)(3), Priyadarsinee L(3), Sastry

GN(4)(5).

Author information:

(1)Centre for Molecular Modelling, CSIR-Indian Institute of Chemical Technology,

Hyderabad, 500007, India.

(2)Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002,

India.

(3)Advanced Computation and Data Sciences Division, CSIR - North East Institute

of Science and Technology, Jorhat, Assam, 785 006, India.

(4)Academy of Scientific and Innovative Research (AcSIR), Ghaziabad, 201002,

India. gnsastry@gmail.com.

(5)Advanced Computation and Data Sciences Division, CSIR - North East Institute

of Science and Technology, Jorhat, Assam, 785 006, India. gnsastry@gmail.com.

Development of potential antitubercular molecules is a challenging task due to

the rapidly emerging drug-resistant strains of Mycobacterium tuberculosis

(M.tb). Structure-based approaches hold greater benefit in identifying

compounds/drugs with desired polypharmacological profiles. These methods can be

employed based on the knowledge of protein binding sites to identify the

complementary ligands. In this study, polypharmacology guided computational drug

repurposing approach was applied to identify potential antitubercular drugs. 20

important druggable protein targets in M.tb were considered from the target

library of Molecular Property Diagnostic Suite-Tuberculosis (MPDSTB-

http://mpds.neist.res.in:8084 ) for virtual screening. FDA approved drugs were

collected, preprocessed and docked in the active sites of the 20 M.tb targets.

The top 300 drug molecules from each target (20 × 300) were filtered-in and

subsequently screened for possible antitubercular and antimycobacterial activity

using PASS tool. Using this approach, 34 drugs with predicted antitubercular and

anti-mycobacterial activity were identified along with good binding affinity

against multiple M.tb targets. Interestingly, 21 out of the 34 identified drugs

are antibiotics while 4 drug molecules (nitrofural, stavudine, quinine and

quinidine) are non-antibiotics showing promising predicted antitubercular

activity. Most of these molecules have the similar privileged antimycobacterial

drugs scaffold. Further drug likeness properties were calculated to get deeper

insights to M.tb lead molecules. Interestingly, it was also observed that the

drugs identified from the study are under different stages of drug discovery

(i.e., in vitro, clinical trials) for the effective treatment of various

diseases including cancer, degenerative diseases, dengue virus infection,

tuberculosis, etc. Krasavin et al., 2017 synthesized nitrofuran analogues with

appreciable MICs (22-23 µM) against M.tb H37Rv. These experiments further add to

the credibility of the drugs identified in this study (TB).

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AG.

DOI: 10.1007/s11030-021-10296-2

PMID: 34468898

**24. J Pharm Pharmacol. 2021 Sep 1:rgab121. doi: 10.1093/jpp/rgab121. Online ahead of print.**

Semi-solid extrusion 3D printing of starch-based soft dosage forms for the

treatment of paediatric latent tuberculosis infection.

Chatzitaki AT(1), Mystiridou E(2), Bouropoulos N(2)(3), Ritzoulis C(4),

Karavasili C(1), Fatouros DG(1).

Author information:

(1)Laboratory of Pharmaceutical Technology, Department of Pharmacy, School of

Health Sciences, Aristotle University of Thessaloniki, Thessaloniki, Greece.

(2)Department of Materials Science, University of Patras, Patras, Greece.

(3)Foundation for Research and Technology Hellas, Institute of Chemical

Engineering and High Temperature Chemical Processes, Patras, Greece.

(4)Department of Food Science and Technology, International Hellenic University,

Thessaloniki, Greece.

**OBJECTIVES:** The development of age-appropriate dosage forms is essential for

effective pharmacotherapy, especially when long-term drug treatment is required,

as in the case of latent tuberculosis infection treatment with up to 9 months of

daily isoniazid (ISO). Herein, we describe the fabrication of starch-based soft

dosage forms of ISO using semi-solid extrusion (SSE) 3D printing.

**METHODS:** Corn starch was used for ink preparation using ISO as model drug. The

inks were characterized physicochemically and their viscoelastic properties were

assessed with rheological analysis. The morphology of the printed dosage forms

was visualized with scanning electron microscopy and their textural properties

were evaluated using texture analysis. Dose accuracy was verified before

in-vitro swelling and dissolution studies in simulated gastric fluid (SGF).

**KEY FINDINGS:** Starch inks were printed with good resolution and high drug dose

accuracy. The printed dosage forms had a soft texture to ease administration in

paediatric patients and a highly porous microstructure facilitating water

penetration and ISO diffusion in SGF, resulting in almost total drug release

within 45 min.

**CONCLUSIONS:** The ease of preparation and fabrication combined with the

cost-effectiveness of the starting materials constitutes SSE 3D printing of

starch-based soft dosage forms a viable approach for paediatric-friendly

formulations in low-resource settings.

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e-mail: journals.permissions@oup.com.

DOI: 10.1093/jpp/rgab121

PMID: 34468746

**25. HIV Med. 2021 Sep 1. doi: 10.1111/hiv.13163. Online ahead of print.**

Improving healthcare for patients with HIV, tuberculosis and hepatitis C in

eastern Europe: a review of current challenges and important next steps.

Kraef C(1)(2)(3), Bentzon A(1), Skrahina A(4), Mocroft A(1)(5), Peters L(1),

Lundgren JD(1)(2), Chkhartishvili N(6)(7), Podlekareva D(1)(2), Kirk O(1)(2).

Author information:

(1)CHIP (Centre of Excellence for Health, Immunity and Infections),

Rigshospitalet, University of Copenhagen, Copenhagen, Denmark.

(2)Department of Infectious Disease, Rigshospitalet, University of Copenhagen,

Copenhagen, Denmark.

(3)Heidelberg Institute of Global Health, University of Heidelberg, Heidelberg,

Germany.

(4)Republican Scientific and Practical Center for Pulmonology and Tuberculosis,

Minsk, Belarus.

(5)Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME),

Institute for Global Health, University College London, London, UK.

(6)Infectious Diseases, AIDS & Clinical Immunology Research Center, Tbilisi,

Georgia.

(7)Caucasus International University, Tbilisi, Georgia.

**OBJECTIVES:** In some eastern European countries, serious challenges exist to meet

the HIV-, tuberculosis (TB)- and hepatitis-related target of the United Nations

Sustainable Development Goals. Some of the highest incidence rates for HIV and

the highest proportion of multi-drug-resistant (MDR) tuberculosis worldwide are

found in the region. The purpose of this article is to review the challenges and

important next steps to improve healthcare for people living with TB, HIV and

hepatitis C (HCV) in eastern Europe.

**METHODS:** References for this narrative review were identified through systematic

searches of PubMed using pre-idientified key word for articles published in

English from January 2000 to August 2020. After screening of titles and

abstracts 37 articles were identified as relevant for this review. Thirty-eight

further articles and sources were identified through searches in the authors'

personal files and in Google Scholar.

**RESULTS:** Up to 50% of HIV/MDR-TB-coinfected individuals in the region die within

2 years of treatment initiation. Antiretroviral therapy (ART) coverage for

people living with HIV (PLHIV) and the proportion virological suppressed are far

below the UNAIDS 90% targets. In theory, access to various diagnostic tests and

treatment of drug-resistant TB exists, but real-life data point towards

inadequate testing and treatment. New treatments could provide elimination of

viral HCV in high-risk populations but few countries have national programmes.

**CONCLUSION:** Some eastern European countries face serious challenges to achieve

the sustainable development goal-related target of 3.3 by 2030, among others, to

end the epidemics of AIDS and tuberculosis. Better integration of healthcare

systems, standardization of health care, unrestricted substitution therapy for

all people who inject drugs, widespread access to drug susceptibility testing,

affordable medicines and a sufficiently sized, well-trained health workforce

could address some of those challenges.

© 2021 British HIV Association.

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PMID: 34468073

**26. Emerg Microbes Infect. 2021 Sep 1:1-32. doi: 10.1080/22221751.2021.1976079.**

**Online ahead of print.**

Global DNA hypomethylation of Alu and LINE-1 transposable elements as an

epigenetic biomarker of anti-tuberculosis drug-induced liver injury.

Udomsinprasert W(1), Sakuntasri W(2), Jittikoon J(1), Chaikledkaew U(3)(4),

Honsawek S(5), Chantratita W(6), Wattanapokayakit S(7), Mahasirimongkol S(7).

Author information:

(1)Department of Biochemistry, Faculty of Pharmacy, Mahidol University, Bangkok

10400, Thailand.

(2)Master of Science Program in Biopharmaceutical Sciences, Department of

Biochemistry, Faculty of Pharmacy, Mahidol University, Bangkok 10400, Thailand.

(3)Social and Administrative Pharmacy Division, Department of Pharmacy, Faculty

of Pharmacy, Mahidol University, Bangkok 10400, Thailand.

(4)Mahidol University Health Technology Assessment (MUHTA) Graduate Program,

Mahidol University, Bangkok 10400, Thailand.

(5)Department of Biochemistry, Osteoarthritis and Musculoskeleton Research Unit,

Faculty of Medicine, Chulalongkorn University, King Chulalongkorn Memorial

Hospital, Thai Red Cross Society, Bangkok 10330, Thailand.

(6)Center for Medical Genomics, Faculty of Medicine, Ramathibodi Hospital,

Mahidol University, Bangkok 10400, Thailand.

(7)Genomic Medicine Centre, Division of Genomic Medicine and Innovation Support,

Department of Medical Sciences, Ministry of Public Health, Nonthaburi 11000,

Thailand.

Despite being highly effective, anti-tuberculosis (TB) drugs often induce

adverse liver injury, anti-TB drug-induced liver injury (ATDILI), leading to

treatment failure given no sensitive and selective ATDILI markers. Herein, we

conducted a case-control association study to determine whether global DNA

methylation of Alu and LINE-1 transposable elements responsible for genomic

stability and transcriptional regulation was correlated with clinical parameters

indicating ATDILI in TB patients and might serve as an ATDILI biomarker. Alu and

LINE-1 methylation levels in blood leukocyte of 130 TB patients (80 ATDILI cases

and 50 non-ATDILI cases) and 100 healthy controls were quantified using

quantitative combined bisulfite restriction analysis. Both TB patients with and

without ATDILI had significantly lower methylation levels of Alu and LINE-1

elements than healthy controls. Compared with non-ATDILI patients, Alu

methylation levels were significantly decreased in ATDILI patients, commensurate

with LINE-1 methylation analysis. Hypomethylation of Alu and LINE-1 measured

within 1-7 days of TB treatment was independently associated with raised levels

of serum aminotransferases assessed within 8-60 days of TB treatment. Receiver

operating characteristic curve analysis uncovered that Alu and LINE-1

methylation levels were both more sensitive and specific for differentiating

ATDILI cases from non-ATDILI cases than serum aminotransferases after starting

TB treatment within 1-7 days. Kaplan-Meier analysis displayed a significant

association between hypomethylation of Alu and LINE-1 elements and an increased

rate of ATDILI occurrence in TB patients. Collectively, global DNA

hypomethylation of Alu and LINE-1 elements would reflect ATDILI progression and

might serve as novel sensitive and specific ATDILI biomarkers.

DOI: 10.1080/22221751.2021.1976079

PMID: 34467830

**27. New Microbes New Infect. 2021 Aug 1;43:100921. doi: 10.1016/j.nmni.2021.100921.**

**eCollection 2021 Sep.**

Beijing genotype of Mycobacterium tuberculosis is associated with extensively

drug-resistant tuberculosis: A global analysis.

Keikha M(1)(2), Majidzadeh M(1)(2).

Author information:

(1)Antimicrobial Resistance Research Center, Mashhad University of Medical

Sciences, Mashhad, Iran.

(2)Department of Microbiology and Virology, Faculty of Medicine, Mashhad

University of Medical Sciences, Mashhad, Iran.

We found that the frequency of Beijing genotype among XDR-TB strains was high.

The data in this study would help guide the TB control program, and we however

need further investigation to confirm the reliability of the present findings.

© 2021 The Author(s).

DOI: 10.1016/j.nmni.2021.100921

PMCID: PMC8383003

PMID: 34466269

**28. BMC Infect Dis. 2021 Aug 31;21(1):891. doi: 10.1186/s12879-021-06593-8.**

Transmission patterns of rifampicin resistant Mycobacterium tuberculosis complex

strains in Cameroon: a genomic epidemiological study.

Merker M(1)(2)(3), Egbe NF(4)(5), Ngangue YR(4), Vuchas C(4), Kohl TA(6), Dreyer

V(6), Kuaban C(7), Noeske J(8), Niemann S(#)(6)(9), Sander MS(#)(4).

Author information:

(1)Molecular and Experimental Mycobacteriology, Research Center Borstel,

Borstel, Germany. mmerker@fz-borstel.de.

(2)Evolution of the Resistome, Research Center Borstel, Borstel, Germany.

mmerker@fz-borstel.de.

(3)German Center for Infection Research, Partner Site

Hamburg-Lübeck-Borstel-Riems, Borstel, Germany. mmerker@fz-borstel.de.

(4)Tuberculosis Reference Laboratory Bamenda, Center for Health Promotion and

Research, Bamenda, Cameroon.

(5)School of Life Sciences, College of Science, University of Lincoln, Lincoln,

England, UK.

(6)Molecular and Experimental Mycobacteriology, Research Center Borstel,

Borstel, Germany.

(7)Faculty of Health Sciences, University of Bamenda, Bamenda, Cameroon.

(8), Bamenda, Cameroon.

(9)German Center for Infection Research, Partner Site

Hamburg-Lübeck-Borstel-Riems, Borstel, Germany.

(#)Contributed equally

**BACKGROUND:** Determining factors affecting the transmission of rifampicin (RR)

and multidrug-resistant (MDR) Mycobacterium tuberculosis complex strains under

standardized tuberculosis (TB) treatment is key to control TB and prevent the

evolution of drug resistance.

**METHODS:** We combined bacterial whole genome sequencing (WGS) and epidemiological

investigations for 37% (n = 195) of all RR/MDR-TB patients in Cameroon

(2012-2015) to identify factors associated with recent transmission.

**RESULTS:** Patients infected with a strain resistant to high-dose isoniazid, and

ethambutol had 7.4 (95% CI 2.6-21.4), and 2.4 (95% CI 1.2-4.8) times increased

odds of being in a WGS-cluster, a surrogate for recent transmission.

Furthermore, age between 30 and 50 was positively correlated with recent

transmission (adjusted OR 3.8, 95% CI 1.3-11.4). We found high drug-resistance

proportions against three drugs used in the short standardized MDR-TB regimen in

Cameroon, i.e. high-dose isoniazid (77.4%), ethambutol (56.9%), and pyrazinamide

(43.1%). Virtually all strains were susceptible to fluoroquinolones, kanamycin,

and clofazimine, and treatment outcomes were mostly favourable (87.5%).

**CONCLUSION:** Pre-existing resistance to high-dose isoniazid, and ethambutol is

associated with recent transmission of RR/MDR strains in our study. A possible

contributing factor for this observation is the absence of universal drug

susceptibility testing in Cameroon, likely resulting in prolonged exposure of

new RR/MDR-TB patients to sub-optimal or failing first-line drug regimens.

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DOI: 10.1186/s12879-021-06593-8

PMCID: PMC8406724

PMID: 34465301

**29. Rev Esc Enferm USP. 2021 Aug 30;55:e20200538. doi:**

**10.1590/1980-220X-REEUSP-2020-0538. eCollection 2021.**

Information system on tuberculosis: data completeness spatial analysis in the

state of Paraná, Brazil.

[Article in English, Portuguese]

Silva MSD(1), Arcoverde MAM(2), Andrade RLP(3), Zilly A(2), Villa TCS(3),

Silva-Sobrinho RA(2).

Author information:

(1)Universidade Estadual do Oeste do Paraná, Programa de Pós-Graduação em Saúde

em Região de Fronteira, Foz do Iguaçu, PR, Brazil.

(2)Universidade Estadual do Oeste do Paraná, Foz do Iguaçu, PR, Brazil.

(3)Universidade de São Paulo, Escola de Enfermagem de Ribeirão Preto, Ribeirão

Preto, SP, Brazil.

**OBJECTIVE:** To analyze the spatiality of completeness of the Information System

on Diseases of Compulsory Declaration of tuberculosis in Paraná state, focusing

on the border region.

**METHOD:** A study composed by the notified cases of the disease treated in Paraná

between 2008 and 2017. The variable completeness was classified as excellent

(<5% of incompleteness), good (5 to <10%), regular (10 to <20%), poor (20% to

50%), and very poor (>50%). Moran global was used for the spatial correlation

and local association was analyzed. Logistic regression was employed to assess

the spatial association of the variables with the border and, for the

significant variables, multiple logistic regression was used. The study abides

by the resolution 510/2016 of the National Health Council.

**RESULTS:** There was a "high-high" correlation for education level, 2- and 6-month

sputum smear in the Eastern health macroregional and "high-high" correlation in

the Northwestern macroregional for 2-month sputum smear and antibiotic

sensitivity testing. There was no spatial association with the border.

**CONCLUSION:** Unsatisfactory completeness was identified in the database and

conglomerates, indicating spatial association of incompleteness of some

variables, but with no relation with the border. There was no worsening of

completeness nor of the case outcomes related to these regions.

DOI: 10.1590/1980-220X-REEUSP-2020-0538

PMID: 34464433 [Indexed for MEDLINE]

**30. PLoS One. 2021 Aug 31;16(8):e0252095. doi: 10.1371/journal.pone.0252095.**

**eCollection 2021.**

Pathways to care and preferences for improving tuberculosis services among

tuberculosis patients in Zambia: A discrete choice experiment.

Kerkhoff AD(1), Kagujje M(2), Nyangu S(2), Mateyo K(3), Sanjase N(2), Chilukutu

L(2), Eshun-Wilson I(4), Geng EH(4), Havlir DV(1), Muyoyeta M(2).

Author information:

(1)Division of HIV, Infectious Diseases and Global Medicine Zuckerberg San

Francisco General Hospital and Trauma Center University of California, San

Francisco, California, United States of America.

(2)Centre for Infectious Disease Research in Zambia, Lusaka, Zambia.

(3)University Teaching Hospital, Department of Internal Medicine, Lusaka,

Zambia.

(4)Division of Infectious Diseases, Washington University School of Medicine,

St. Louis, Missouri, United States of America.

**BACKGROUND:** Delays in the diagnosis of tuberculosis (TB) contribute to a

substantial proportion of TB-related mortality, especially among people living

with HIV (PLHIV). We sought to characterize the diagnostic journey for

HIV-positive and HIV-negative patients with a new TB diagnosis in Zambia, to

understand drivers of delay, and characterize their preferences for service

characteristics to inform improvements in TB services.

**METHODS:** We assessed consecutive adults with newly microbiologically-confirmed

TB at two public health treatment facilities in Lusaka, Zambia. We administered

a survey to document critical intervals in the TB care pathway (time to initial

care-seeking, diagnosis and treatment initiation), identify bottlenecks and

their reasons. We quantified patient preferences for a range of characteristics

of health services using a discrete choice experiment (DCE) that assessed 7

attributes (distance, wait times, hours of operation, confidentiality, sex of

provider, testing incentive, TB test speed and notification method).

**RESULTS:** Among 401 patients enrolled (median age of 34 years, 68.7% male, 46.6%

HIV-positive), 60.9% and 39.1% were from a first-level and tertiary hospital,

respectively. The median time from symptom onset to receipt of TB treatment was

5.0 weeks (IQR: 3.6-8.0) and was longer among HIV-positive patients seeking care

at a tertiary hospital than HIV-negative patients (6.4 vs. 4.9 weeks, p =

0.002). The time from symptom onset to initial presentation for evaluation

accounted for the majority of time until treatment initiation (median 3.0 weeks,

IQR: 1.0-5.0)-an important minority of 11.0% of patients delayed care-seeking ≥8

weeks. The DCE found that patients strongly preferred same-day TB test results

(relative importance, 37.2%), facilities close to home (18.0%), and facilities

with short wait times (16.9%). Patients were willing to travel to a facility up

to 7.6 kilometers further away in order to access same-day TB test results.

Preferences for improving current TB services did not differ according to HIV

status.

**CONCLUSIONS:** Prolonged intervals from TB symptom onset to treatment initiation

were common, especially among PLHIV, and were driven by delayed health-seeking.

Addressing known barriers to timely diagnosis and incorporating patients'

preferences into TB services, including same-day TB test results, may facilitate

earlier TB care engagement in high burden settings.

DOI: 10.1371/journal.pone.0252095

PMCID: PMC8407587

PMID: 34464392

**31. ACS Biomater Sci Eng. 2021 Aug 31. doi: 10.1021/acsbiomaterials.1c00807. Online**

**ahead of print.**

Mesoporous Silica Nanoparticles Improve Oral Delivery of Antitubercular Bicyclic

Nitroimidazoles.

Ang CW(1)(2), Tan L(3)(4), Qu Z(5)(6), West NP(3)(4), Cooper MA(1)(4), Popat

A(5)(6), Blaskovich MAT(1)(4).

Author information:

(1)Centre for Superbug Solutions, Institute for Molecular Bioscience, The

University of Queensland, St Lucia, Queensland 4072, Australia.

(2)School of Science, Monash University Malaysia, Subang Jaya 47500, Selangor,

Malaysia.

(3)School of Chemistry and Molecular Bioscience, The University of Queensland,

St Lucia, Queensland 4072, Australia.

(4)Australian Infectious Diseases Research Centre, St Lucia, Queensland 4067,

Australia.

(5)School of Pharmacy, The University of Queensland, Woolloongabba, Queensland

4102, Australia.

(6)Mater Research Institute and Translational Research Institute, The University

of Queensland, Woolloongabba, Queensland 4102, Australia.

Pretomanid and MCC7433, a novel nitroimidazopyrazinone analog, are promising

antitubercular agents that belong to the bicyclic nitroimidazole family. Despite

possessing high cell permeability, they suffer from poor aqueous solubility and

require specialized formulations in order to be orally bioavailable. To address

this limitation, we investigated the use of mesoporous silica nanoparticles

(MCM-41) as drug carriers. MCM-41 nanoparticles were synthesized using a sol-gel

method, and their surface was further modified with amine and phosphonate

groups. A simple rotary evaporation method was used to incorporate the compounds

of interest into the nanoparticles, leading to a high encapsulation efficiency

of ≥86% with ∼10% loading (w/w). An overall significant improvement of

solubility was also observed, and the pharmacological activity of pretomanid and

MCC7433 was fully retained when tested in vitro against Mycobacterium

tuberculosis using these nanocarriers. Amino-functionalized MCM-41 nanoparticles

were found to enhance the systemic exposure of MCC7433 in mice (1.3-fold higher

Cmax) compared to MCC7433 alone. The current work highlights the potential of

using nanoparticles such as mesoporous silica as a carrier for oral delivery of

poorly soluble antibacterial agents against tuberculosis.

DOI: 10.1021/acsbiomaterials.1c00807

PMID: 34464089

**32. J Biomol Struct Dyn. 2021 Aug 31:1-9. doi: 10.1080/07391102.2021.1969284. Online**

**ahead of print.**

Insights into the mutations leading to capreomycin resistance in

S-adenosyl-L-methionine binding motif in TlyA from Mycobacterium tuberculosis.

Ali W(1), Jamal S(1), Grover A(2), Grover S(1).

Author information:

(1)Department of Molecular Medicine, Jamia Hamdard, New Delhi, India.

(2)School of Biotechnology, Jawaharlal Nehru University, New Delhi, India.

Capreomycin is a second line antibiotic used for the treatment of drug resistant

Tuberculosis (TB), primary reason of death from a solo infectious organism,

Mycobacterium tuberculosis (M.tb). Capreomycin targets the ribosome of bacteria

and is known to bind at the interface where the large and small ribosomal

subunits interact in M.tb using an S-Adenosyl Methionine (SAM) dependent

methyltransferase, TlyA (Rv1794). Besides the methyltransferase activity, TlyA

has also been found to show substantial haemolytic activity. The dual activity

of TlyA highlights its crucial role in pathogenesis and virulence of M.tb. In

the present study, docking and molecular dynamics (MD) simulations were carried

out to explore the impact of mutations in a conserved SAM binding motif,

90GASTG94, on the affinity of TlyA enzyme for SAM. Two already reported

mutations, A91E and S92L, and the remaining wild type residues, Gly90, Thr93,

Gly94 mutated to alanine were taken into consideration resulting in a total of

six systems, wild type + SAM, G90A + SAM, A91E + SAM, S92L + SAM, T93A + SAM and

G94A + SAM that were subjected to 100 ns MD simulations. Docking scores and MD

simulations analyses revealed that in contrast to wild type, mutants reduced the

affinity of SAM for TlyA with most prominent effect observed in case of alanine

mutants. Mutations also led to the loss of hydrogen bond and hydrophobic

interactions and large-scale movement of atoms evident from the principal

component analyses indicating their destabilizing impact on TlyA. The present

study gives insights into influence of mutations on binding of SAM to TlyA in

M.tb and promoting capreomycin resistance.Communicated by Ramaswamy H. Sarma.

DOI: 10.1080/07391102.2021.1969284

PMID: 34463210

**33. Pol Arch Intern Med. 2021 Aug 30;131(7-8):615-616. doi: 10.20452/pamw.16065.**

**Epub 2021 Aug 30.**

The present role of the thoracic surgeon in the diagnostic workup of

tuberculosis.

Petrella F.

Comment on

 Pol Arch Intern Med. 2021 Aug 30;131(7-8):633-642.

DOI: 10.20452/pamw.16065

PMID: 34463081

**34. Sci Rep. 2021 Aug 30;11(1):17387. doi: 10.1038/s41598-021-96956-7.**

Whole genome sequencing of clinical samples reveals extensively drug resistant

tuberculosis (XDR TB) strains from the Beijing lineage in Nigeria, West Africa.

Olawoye IB(1)(2), Uwanibe JN(1)(2), Kunle-Ope CN(3), Davies-Bolorunduro OF(3),

Abiodun TA(3), Audu RA(3), Salako BL(3), Happi CT(4)(5).

Author information:

(1)African Centre of Excellence for Genomics of Infectious Diseases (ACEGID),

Redeemer's University, Ede, Osun State, Nigeria.

(2)Department of Biological Sciences, Faculty of Natural Sciences, Redeemer's

University, Ede, Osun State, Nigeria.

(3)Centre for Tuberculosis Research (CTBR), Microbiology Department, Nigerian

Institute of Medical Research (NIMR), Yaba, Lagos State, Nigeria.

(4)African Centre of Excellence for Genomics of Infectious Diseases (ACEGID),

Redeemer's University, Ede, Osun State, Nigeria. happic@run.edu.ng.

(5)Department of Biological Sciences, Faculty of Natural Sciences, Redeemer's

University, Ede, Osun State, Nigeria. happic@run.edu.ng.

Multi-drug (MDR) and extensively drug-resistant (XDR) tuberculosis (TB)

continues to be a global public health problem especially in high TB burden

countries like Nigeria. Many of these cases are undetected and go on to infect

high risk individuals. Clinical samples from positive rifampicin resistant

Xpert®MTB/Rif assay were subjected to direct whole genome sequencing and

bioinformatics analysis to identify the full antibiotics resistance and lineage

profile. We report two (2) XDR TB samples also belonging to the

East-Asian/Beijing family of lineage 2 Mycobacterium tuberculosis complex from

clinical samples in Nigeria. Our findings further reveal the presence of

mutations that confer resistance to first-line drugs (rifampicin, isoniazid,

ethambutol and pyrazanimide), second-line injectables (capreomycin,

streptomycin, kanamycin and/or amikacin) and at least one of the

fluoroquinolones (ofloxacin, moxifloxacin, levofloxacin and/or ciprofloxacin) in

both samples. The genomic sequence data from this study not only provide the

first evidence of XDR TB in Nigeria and West Africa, but also emphasize the

importance of WGS in accurately detecting MDR and XDR TB, to ensure adequate and

proper management treatment regimens for affected individuals. This will greatly

aid in preventing the spread of drug resistance TB in high burden countries.

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DOI: 10.1038/s41598-021-96956-7

PMCID: PMC8405707

PMID: 34462504

**35. Genome Med. 2021 Aug 30;13(1):138. doi: 10.1186/s13073-021-00953-4.**

GenTB: A user-friendly genome-based predictor for tuberculosis resistance

powered by machine learning.

Gröschel MI(1), Owens M(1), Freschi L(1), Vargas R Jr(1)(2), Marin MG(1)(2),

Phelan J(3), Iqbal Z(4), Dixit A(1)(5), Farhat MR(6)(7).

Author information:

(1)Department of Biomedical Informatics, Harvard Medical School, Boston, MA,

USA.

(2)Department of Systems Biology, Harvard Medical School, Boston, MA, USA.

(3)Faculty of Infectious and Tropical Diseases, London School of Hygiene &

Tropical Medicine, London, WC1E 7HT, UK.

(4)European Bioinformatics Institute, Hinxton, Cambridge, CB10 ISD, UK.

(5)Division of Infectious Diseases, Boston Children's Hospital, Boston, MA, USA.

(6)Department of Biomedical Informatics, Harvard Medical School, Boston, MA,

USA. maha\_farhat@hms.harvard.edu.

(7)Division of Pulmonary and Critical Care Medicine, Massachusetts General

Hospital, Boston, MA, USA. maha\_farhat@hms.harvard.edu.

**BACKGROUND:** Multidrug-resistant Mycobacterium tuberculosis (Mtb) is a

significant global public health threat. Genotypic resistance prediction from

Mtb DNA sequences offers an alternative to laboratory-based drug-susceptibility

testing. User-friendly and accurate resistance prediction tools are needed to

enable public health and clinical practitioners to rapidly diagnose resistance

and inform treatment regimens.

**RESULTS:** We present Translational Genomics platform for Tuberculosis (GenTB), a

free and open web-based application to predict antibiotic resistance from

next-generation sequence data. The user can choose between two potential

predictors, a Random Forest (RF) classifier and a Wide and Deep Neural Network

(WDNN) to predict phenotypic resistance to 13 and 10 anti-tuberculosis drugs,

respectively. We benchmark GenTB's predictive performance along with leading TB

resistance prediction tools (Mykrobe and TB-Profiler) using a ground truth

dataset of 20,408 isolates with laboratory-based drug susceptibility data. All

four tools reliably predicted resistance to first-line tuberculosis drugs but

had varying performance for second-line drugs. The mean sensitivities for

GenTB-RF and GenTB-WDNN across the nine shared drugs were 77.6% (95% CI

76.6-78.5%) and 75.4% (95% CI 74.5-76.4%), respectively, and marginally higher

than the sensitivities of TB-Profiler at 74.4% (95% CI 73.4-75.3%) and Mykrobe

at 71.9% (95% CI 70.9-72.9%). The higher sensitivities were at an expense of ≤

1.5% lower specificity: Mykrobe 97.6% (95% CI 97.5-97.7%), TB-Profiler 96.9%

(95% CI 96.7 to 97.0%), GenTB-WDNN 96.2% (95% CI 96.0 to 96.4%), and GenTB-RF

96.1% (95% CI 96.0 to 96.3%). Averaged across the four tools, genotypic

resistance sensitivity was 11% and 9% lower for isoniazid and rifampicin

respectively, on isolates sequenced at low depth (< 10× across 95% of the

genome) emphasizing the need to quality control input sequence data before

prediction. We discuss differences between tools in reporting results to the

user including variants underlying the resistance calls and any novel or

indeterminate variants **CONCLUSIONS:** GenTB is an easy-to-use online tool to

rapidly and accurately predict resistance to anti-tuberculosis drugs. GenTB can

be accessed online at https://gentb.hms.harvard.edu , and the source code is

available at https://github.com/farhat-lab/gentb-site .

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DOI: 10.1186/s13073-021-00953-4

PMCID: PMC8407037

PMID: 34461978

**36. Asian Spine J. 2021 Sep 1. doi: 10.31616/asj.2021.0137. Online ahead of print.**

Epidemiological Insights from 1,652 Patients with Spinal Tuberculosis Managed at

a Single Center: A Retrospective Review of 5-Year Data.

Garg B(1), Mehta N(1), Mukherjee RN(1), Swamy AM(1), Siamwala BS(1), Malik G(1).

Author information:

(1)Department of Orthopaedics, All India Institute of Medical Sciences, New

Delhi, India.

STUDY DESIGN: Retrospective cohort.

**PURPOSE:** To report the demographic characteristics, clinico-radiological

presentation, laboratory findings, and outcomes of "middlepath" treatment in

patients with spinal tuberculosis from a single public healthcare facility in a

developing country.

**OVERVIEW OF LITERATURE:** Tuberculosis is a global health problem that is endemic

in developing countries and undergoing resurgence in developed ones. Spinal

tuberculosis can cause disabling back pain, progressive deformity, and

neurological involvement. However, there is a lack of large-scale

epidemiological studies quantifying the size and severity of the problem of

spinal tuberculosis.

**METHODS:** Hospital records of spinal tuberculosis patients treated at a single

center over a period of 5 years were retrospectively reviewed. A diagnosis of

spinal tuberculosis was based on standard clinical, radiological,

microbiological, and histopathological evidence. Patients were treated in

accordance with the "middle-path" regimen; surgery was reserved for selective

indications.

**RESULTS:** A total of 1,652 patients were included. Their median age was 32.4

years, with 53% being male. Axial pain (98%) was the most common presenting

symptom; 19% of patients had neurological deficit. Lumbar spine (37%) was the

most common site of involvement, with a paradiscal pattern (82%) of involvement

predominating. Multi-level involvement was seen in 19% of patients; skip lesions

were noted in 2.8%. Transpedicular biopsy was performed in 667 patients; at

least one tissue test was diagnostic of tuberculosis in 65% of patients.

Forty-four patients had drug resistance to rifampicin. Surgery was required in

10.5% of patients. The "middle-path" regimen was associated with high compliance

and significant improvements in pain (Visual Analog Scale score) and function

(36-Item Short Form Health Survey).

**CONCLUSIONS:** Our findings confirm the widespread prevalence of spinal

tuberculosis and describe various epidemiological characteristics of a large

sample of spinal tuberculosis patients. Adoption of the "middle-path" regimen is

associated with high compliance and favorable outcomes in spinal tuberculosis.

DOI: 10.31616/asj.2021.0137

PMID: 34461687

**37. Am J Respir Crit Care Med. 2021 Aug 30. doi: 10.1164/rccm.202107-1795ED. Online**

**ahead of print.**

Characterization of Air Pollution Exposures as Risk Factors for Tuberculosis

Infection.

Davis JL(1), Checkley W(2).

Author information:

(1)Yale School of Public Health, New Haven, Connecticut, United States;

Lucian.Davis@yale.edu.

(2)Johns Hopkins University, 1466, Division of Pulmonary and Critical Care,

School of Medicine, Baltimore, Maryland, United States.

DOI: 10.1164/rccm.202107-1795ED

PMID: 34461027

**38. PLoS One. 2021 Aug 30;16(8):e0247745. doi: 10.1371/journal.pone.0247745.**

**eCollection 2021.**

The monocyte-to-lymphocyte ratio: Sex-specific differences in the tuberculosis

disease spectrum, diagnostic indices and defining normal ranges.

Buttle TS(1), Hummerstone CY(1), Billahalli T(1), Ward RJB(1), Barnes KE(2),

Marshall NJ(2), Spong VC(1), Bothamley GH(1)(3)(4).

Author information:

(1)Department of Respiratory Medicine, Homerton University Hospital, London,

United Kingdom.

(2)Microbiology Department, Homerton University Hospital, London, United

Kingdom.

(3)Department of Immunobiology, Blizard Institute, Barts and The London School

of Medicine and Dentistry, Queen Mary University of London, London, United

Kingdom.

(4)Department of Infectious and Tropical Diseases, London School of Hygiene and

Tropical Medicine, London, United Kingdom.

**BACKGROUND:** The monocyte-to-lymphocyte ratio (MLR) has been advocated as a

biomarker in tuberculosis. Our objective was to evaluate its clinical value and

associations.

**METHODS:** Blood counts, inflammatory markers and clinical parameters were

measured in patients with and those screened for tuberculosis. Complete blood

counts (CBCs) from a multi-ethnic population aged 16 to 65 years were evaluated;

a sub-group with normal hematological indices was used to define the range of

MLRs.

**RESULTS:** Multivariate analysis in proven tuberculosis (n = 264) indicated MLR

associated with low serum albumin, high white cell counts and a positive

culture; values were higher in sputum smear-positive pulmonary tuberculosis

(S+PTB). Analysis in S+PTB (n = 296) showed higher MLRs in males and those with

high neutrophil counts, low serum albumin and high C-reactive protein. The

diagnostic value of MLRs was assessed by comparing notified patients with TB (n

= 264) with denotified cases (n = 50), active case-finding in non-contacts (TB n

= 111 and LTBI n = 373) and contacts of S+PTB (n = 149) with S+PTB found at

screening (n = 75). Sensitivities and specificities ranged from 58.0-62.5% and

50.0-70.0% respectively for optimal cut-off values, defined by ROC curves. In

CBCs obtained over one month, ratios correlated with neutrophil counts (ρ =

0.48, P<0.00001, n = 14,573; MLR = 0.45 at 8-8.9 x 109/L) and were higher in

males than females (P<0.0001). The MLR range (mean ± 2SD) in those with normal

hematological indices (n = 3921: females 0.122-0.474; males 0.136-0.505)

paralleled LTBI MLRs. Ratios did not predict death (n = 29) nor response to

treatment (n = 178 S+PTB with follow-up CBCs). Ratios were higher in males than

female in the 16-45 years age group, where immune differences due to sex

hormones are likely greatest.

**CONCLUSIONS:** Severe tuberculosis and male sex associated with high MLRs; the

same variables likely affect the performance of other biomarkers. The ratio

performed poorly as a clinical aid.

DOI: 10.1371/journal.pone.0247745

PMCID: PMC8405018

PMID: 34460817

**39. Antimicrob Agents Chemother. 2021 Aug 30:AAC0036421. doi: 10.1128/AAC.00364-21.**

**Online ahead of print.**

Rifampicin mono-resistant tuberculosis is not the same as multidrug-resistant

tuberculosis: a descriptive study from Khayelitsha, South Africa.

Salaam-Dreyer Z(1), Streicher EM(2), Sirgel FA(2), Menardo F(3)(4), Borrell

S(3)(4), Reinhard M(3)(4), Doetsch A(3)(4), Cudahy PGT(5), Mohr-Holland E(6),

Daniels J(6), Dippenaar A(7), Nicol MP(8), Gagneux S(3)(4), Warren RM(2), Cox

H(1)(9).

Author information:

(1)Division of Medical Microbiology, Department of Pathology, University of Cape

Town, South Africa.

(2)DST/NRF Centre of Excellence for Biomedical Tuberculosis Research/SAMRC

Centre for Tuberculosis Research, Division of Molecular Biology and Human

Genetics, Faculty of Medicine and Health Sciences, Stellenbosch University,

South Africa.

(3)Swiss Tropical and Public Health Institute, Basel Switzerland.

(4)University of Basel, Basel, Switzerland.

(5)Section of Infectious Diseases, Department of Internal Medicine, Yale School

of Medicine, New Haven, CT, USA.

(6)Médecins Sans Frontières, Khayelitsha, Cape Town, South Africa.

(7)Tuberculosis Omics Research Consortium, Family Medicine and Population

Health, Institute of Global Health, Faculty of Medicine and Health Sciences,

University of Antwerp, Antwerp, Belgium.

(8)Division of Infection and Immunity, School of Biomedical Sciences, University

of Western Australia, Perth, Australia.

(9)Institute of Infectious Disease and Molecular Medicine and Wellcome centre

for Infectious Disease Research, University of Cape Town, South Africa.

Rifampicin mono-resistant TB (RMR-TB, rifampicin resistance and isoniazid

susceptibility) constitutes 38% of all rifampicin-resistant TB (RR-TB) in South

Africa and is increasing. We aimed to compare RMR-TB with multidrug-resistant TB

(MDR-TB) within a high TB, RR-TB and HIV burden setting. Patient-level clinical

data and stored RR-TB isolates from 2008-2017 with available whole genome

sequencing (WGS) data were used to describe risk factors associated with RMR-TB

and to compare rifampicin-resistance (RR) conferring mutations between RMR-TB

and MDR-TB. A subset of isolates with particular RR-conferring mutations were

subjected to semi-quantitative rifampicin phenotypic drug susceptibility

testing. Among 2,041 routinely diagnosed RR-TB patients, 463 (22.7%) had RMR-TB.

HIV-positive individuals (adjusted Odds Ratio 1.4, 95% CI 1.1-1.9) and diagnosis

between 2013-2017 versus 2008-2012 (aOR 1.3, 1.1-1.7) were associated with

RMR-TB. Among 1,119 (54.8%) patients with available WGS data showing RR-TB,

significant differences in the distribution of rpoB RR-conferring mutations

between RMR-TB and MDR-TB isolates were observed. Mutations associated with

high-level RR were more commonly found among MDR-TB isolates (811/889, 90.2%

versus 162/230, 70.4% among RMR-TB, p<0.0001). In particular, the rpoB L430P

mutation, conferring low-level RR, was identified in 32/230 (13.9%) RMR-TB

versus 10/889 (1.1%) in MDR-TB (p<0.0001). Among 10 isolates with an rpoB L430P

mutation, 7 were phenotypically susceptible using the critical concentration of

0.5 μg/ml (range 0.125-1 μg/ml). The majority (215/230, 93.5%) of RMR-TB

isolates showed susceptibility to all other TB drugs, highlighting the potential

benefits of WGS for simplified treatment. These data suggest that the evolution

of RMR-TB differs from MDR-TB with a potential contribution from HIV infection.

DOI: 10.1128/AAC.00364-21

PMID: 34460307

**40. Antimicrob Agents Chemother. 2021 Aug 30:AAC0116421. doi: 10.1128/AAC.01164-21.**

**Online ahead of print.**

The role of epistasis in amikacin, kanamycin, bedaquiline, and clofazimine

resistance in Mycobacterium tuberculosis complex.

Vargas R Jr(1)(2), Freschi L(2), Spitaleri A(3), Tahseen S(4), Barilar I(5)(6),

Niemann S(5)(6), Miotto P(3), Cirillo DM(3), Köser CU(7), Farhat MR(2)(8).

Author information:

(1)Department of Systems Biology, Harvard Medical School, Boston, USA.

(2)Department of Biomedical Informatics, Harvard Medical School, Boston, USA.

(3)Emerging Bacterial Pathogens Unit, IRCCS San Raffaele Scientific Institute,

Milan, Italy.

(4)National TB Reference laboratory, National TB Control Program, Islamabad,

Pakistan.

(5)German Center for Infection Research, Partner site

Hamburg-Lübeck-Borstel-Riems, Borstel, Germany.

(6)Molecular and Experimental Mycobacteriology, Research Center Borstel,

Borstel, Germany.

(7)Department of Genetics, University of Cambridge, Cambridge, UK.

(8)Pulmonary and Critical Care Medicine, Massachusetts General Hospital, Boston,

USA.

Antibiotic resistance among bacterial pathogens poses a major global health

threat. M. tuberculosis complex (MTBC) is estimated to have the highest

resistance rates of any pathogen globally. Given the slow growth rate and the

need for a biosafety level 3 laboratory, the only realistic avenue to scale up

drug susceptibility testing (DST) for this pathogen is to rely on genotypic

techniques. This raises the fundamental question of whether a mutation is a

reliable surrogate for phenotypic resistance or whether the presence of a second

mutation can completely counteract its effect, resulting in major diagnostic

errors (i.e. systematic false resistance results). To date, such epistatic

interactions have only been reported for streptomycin that is now rarely used.

By analyzing more than 31,000 MTBC genomes, we demonstrated that the eis C-14T

promoter mutation, which is interrogated by several genotypic DST assays

endorsed by the World Health Organization, cannot confer resistance to amikacin

and kanamycin if it coincides with loss-of-function (LoF) mutations in the

coding region of eis. To our knowledge, this represents the first definitive

example of antibiotic reversion in MTBC. Moreover, we raise the possibility that

mmpR (Rv0678) mutations are not valid markers of resistance to bedaquiline and

clofazimine if these coincide with a LoF mutation in the efflux pump encoded by

mmpS5 (Rv0677c) and mmpL5 (Rv0676c).

DOI: 10.1128/AAC.01164-21

PMID: 34460306

**41. Antimicrob Agents Chemother. 2021 Aug 30:AAC0141821. doi: 10.1128/AAC.01418-21.**

**Online ahead of print.**

Impact of dose, duration and immune status on efficacy of ultrashort telacebec

regimens in mouse models of Buruli ulcer.

Komm O(1)(2), Almeida DV(1), Converse PJ(1), Omansen TF(2), Nuermberger EL(1).

Author information:

(1)Center for Tuberculosis Research, Department of Medicine, Johns Hopkins

University, Baltimore, Maryland, USA.

(2)Department of Tropical Medicine, Bernhard Nocht Institute for Tropical

Medicine & I. Department of Medicine, University Medical Center

Hamburg-Eppendorf, Hamburg, Germany.

Telacebec (Q203) is a new anti-tuberculosis drug in clinical development with

extremely potent activity against Mycobacterium ulcerans, the causative agent of

Buruli ulcer (BU). The potency of Q203 has prompted investigation of its

potential role in ultra-short, even single-dose, treatment regimens for BU in

mouse models. However, the relationships of Q203 dose, dose schedule, duration

and host immune status to treatment outcomes remain unclear, as does the risk of

emergence of drug resistance with Q203 monotherapy. In the present study, we

used mouse footpad infection models in immunocompetent BALB/c and

immunocompromised SCID-beige mice to compare different Q203 doses, dosing

schedules and treatment durations ranging from 1 day to 2 weeks, on long-term

outcomes. We also tested whether combining Q203 with a second drug can increase

efficacy. Overall, efficacy depended on total dose more than duration. Total

doses of 5-20 mg/kg rendered nearly all BALB/c mice culture-negative 13-15 weeks

post-treatment without selection of Q203-resistant bacteria. Addition of a

second drug did not significantly increase efficacy. Although less potent in

SCID-beige mice, Q203 still rendered the majority of footpads culture-negative

at total doses of 10-20 mg/kg. Q203 resistance was identified in relapse

isolates from some SCID-beige mice receiving monotherapy but not those receiving

Q203 combined with bedaquiline or clofazimine. Overall, these results support

the potential of Q203 monotherapy for single-dose or other ultra-short therapy

for BU, although highly immunocompromised hosts may require higher doses or

durations and/or combination therapy.

DOI: 10.1128/AAC.01418-21

PMID: 34460302

**42. Glob Public Health. 2021 Aug 29:1-13. doi: 10.1080/17441692.2021.1965182. Online ahead of print.**

'If not for this support, I would have left the treatment!': Qualitative study

exploring the role of social support on medication adherence among pulmonary

tuberculosis patients in Western India.

Nirmal A(1), Kuzmik A(2), Sznajder K(3), Lengerich E(3), Fredrick NB(4), Chen

M(5), Hwang W(3), Patil R(6), Shaikh B(7).

Author information:

(1)Population Health Sciences Department, Harrisburg University of Science and

Technology, Harrisburg, USA.

(2)Department of Nursing, Penn State College of Nursing, University Park, USA.

(3)Department of Public Health Sciences, Penn State College of Medicine,

Hershey, USA.

(4)Department of Family and Community Medicine, Penn State College of Medicine,

Hershey, USA.

(5)Global Health Center and Department of Opthalmology, Penn State College of

Medicine, Hershey, USA.

(6)Mauli Hospital, Bhiwandi, India.

(7)Revised National Tuberculosis Control Program of India, Indira Gandhi

Memorial Hospital, Bhiwandi, India.

Social support has been identified as a significant factor in addressing

treatment barriers and facilitating treatment adherence. Using a descriptive

design, this qualitative study aims at sharing personal feelings and social

support-related experiences among pulmonary tuberculosis (TB) patients in

Western India. A semi-structured interview guide was designed, and thirty-seven

in-depth interviews were conducted. Descriptive thematic analysis was employed

for reporting the themes and the results. The participants highlighted diverse

social support experiences like empathy, compassion, trust, neglect, tangible

aid, strained relationships with in-laws, health provider's support, strength,

and motivation which influences their treatment adherent behaviour. Contrasting

differences of social support experiences among adherent and non-adherent TB

patients were also reported. The study has important ramifications for

developing patient-centric social support intervention strategies, TB policy,

and practice. The study has shown, 'if not for this support', patients would

have left the treatment, and it is mainly because this debilitating disease robs

people of their physical, social, economic, psychological, and emotional

well-being far beyond the period when treatment is being administered. However,

we resonate that addressing social support is not the only way, and TB

elimination overall will require an optimal mix of enhanced biomedical, social,

economic, and policy interventions.

DOI: 10.1080/17441692.2021.1965182

PMID: 34459366

**43. S Afr J Psychol. 2021 Sep 1;51(3):409-421. doi: 10.1177/0081246320962729. Epub**

**2020 Oct 12.**

Caregiver-child separation during tuberculosis hospitalisation: a qualitative

study in South Africa.

Meyerson KA(1), Hoddinott G(1), Garcia-Prats AJ(1), Tomlinson M(2)(3).

Author information:

(1)Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty

of Medicine and Health Sciences, Stellenbosch University, South Africa.

(2)Institute for Life Course Health Research, Department of Global Health,

Stellenbosch University, South Africa.

(3)School of Nursing and Midwifery, Queens University, UK.

There are an estimated 32,000 incident cases of multidrug-resistant tuberculosis

in children globally each year. Extended hospitalisation is often required to

ensure optimal adherence to the complex multidrug-resistant tuberculosis

treatment regimen. Hospitalisation usually results in caregiver-child separation

which is known to cause psychological difficulties in children. We explored

caregivers' and health workers' perceptions of the effects of caregiver-child

separation during hospitalisation for tuberculosis in the Western Cape. We

conducted semi-structured interviews with health workers (n = 7) and caregivers

(n = 14) of children who were receiving multidrug-resistant tuberculosis

treatment. All interviews were audio-recorded, transcribed, and translated. We

used thematic analysis to organise and interpret the data. We identified three

themes: (1) multidrug-resistant tuberculosis treatment was a distressing

experience for children, caregivers, and health workers; (2) children's

behavioural states during and post-hospitalisation (e.g., crying, aggression,

hyperactivity, and withdrawal) were suggestive of their distress; and (3)

caregivers and health workers used strategies, such as deception, threat, and

the prioritisation of biomedical health over psychological health as a means to

manage their own as well as the children's distress. This article presents novel

research on the dynamics involved in caregiver-child separation as a result of

multidrug-resistant tuberculosis treatment in South Africa. We highlight that

the challenges of caregiver-child separation intersected with predisposing

factors related to the social adversity that families affected by childhood

tuberculosis experience. Delivery models that facilitate outpatient

community-based care should be prioritised and a more structured form of

psychological support should be implemented for those who still require

hospitalisation.

DOI: 10.1177/0081246320962729

PMCID: PMC8389357

PMID: 34456393

**44. Surgery. 2021 Sep;170(3):e11. doi: 10.1016/j.surg.2021.03.018. Epub 2021 Apr 18.**

Intrahepatic arterial pseudoaneurysm secondary to lymph node tuberculosis.

Sana L(1), Imen R(2), Faouzi C(3).

Author information:

(1)Department of Surgery, Faculty of Medicine of Tunis, University of Tunis El

Manar, Mahmoud El Matri Hospital, Ariana, Tunisia. Electronic address:

sanalandolsi9@gmail.com.

(2)Department of Radiology, Faculty of Medicine of Tunis, University of Tunis El

Manar, Mahmoud El Matri Hospital, Ariana, Tunisia. Electronic address:

https://twitter.com/imen\_ridene.

(3)Department of Surgery, Faculty of Medicine of Tunis, University of Tunis El

Manar, Mahmoud El Matri Hospital, Ariana, Tunisia. Electronic address:

https://twitter.com/faouzi\_chebbi.

DOI: 10.1016/j.surg.2021.03.018

PMID: 34455994

**45. CEN Case Rep. 2021 Aug 29. doi: 10.1007/s13730-021-00641-7. Online ahead of**

**print.**

Membranous nephropathy in a patient with pulmonary tuberculosis infection and

lung adenocarcinoma: a case report.

Morimoto N(1), Nagahama K(2), Tsuura Y(3), Terai A(4), Tanabe M(4), Otani M(4),

Shioji S(4), Hirasawa S(4), Aki S(4), Aoyagi M(4), Tanaka H(4).

Author information:

(1)Department of Nephrology, Yokosuka Kyosai Hospital, 1-16 Yonegahamadori,

Yokosuka, Kanagawa, 238-8558, Japan. nobumorimoto836@gmail.com.

(2)Department of Pathology, Kyorin University School of Medicine, Mitaka, Tokyo,

Japan.

(3)Department of Pathology, Yokosuka Kyosai Hospital, Yokosuka, Kanagawa, Japan.

(4)Department of Nephrology, Yokosuka Kyosai Hospital, 1-16 Yonegahamadori,

Yokosuka, Kanagawa, 238-8558, Japan.

We report a case of membranous nephropathy (MN) in a patient with tuberculosis

infection and lung adenocarcinoma. A 50-year-old Filipino woman underwent a

renal biopsy for the evaluation of proteinuria and hematuria. Immunofluorescence

analysis revealed positive staining of IgG in the glomerular basement membrane

and mesangial matrices, while electron microscopy demonstrated the presence of

sub-epithelial deposits, suggesting MN. To screen for secondary causes of MN, we

conducted a computed tomography (CT) scan of the chest and abdomen, which

revealed a ground-glass opacity in the middle lobe of the right lung and an

enlarged paraaortic lymph node. A T-SPOT test was positive, suggesting the

possibility of a latent tuberculosis infection, as she was asymptomatic. A

follow-up chest CT scan showed persistent presence of the ground-glass

opacities, suggesting a non-infectious cause. Video-assisted thoracoscopic

resection of the middle right lobe and partial resection of the lower right lobe

were performed because the possibility of lung cancer could not be excluded.

Notably, pathological analysis of the lung revealed adenocarcinoma in the middle

lobe and epithelioid granuloma in the lower lobe, suggesting an active

tuberculosis infection. One month after surgery, anti-tuberculosis treatment was

initiated. Thereafter, her proteinuria, which had increased to 6 g/gCre

preoperatively, began to decrease. Five months after surgery, the patient

achieved complete remission. The speed of remission suggests that tuberculosis

likely played a primary role in the etiology of MN. Our case underscores the

importance of screening tests for infections and malignancies in patients with

MN, even if suggestive symptoms are absent.

© 2021. Japanese Society of Nephrology.

DOI: 10.1007/s13730-021-00641-7

PMID: 34455551

**46. Trop Med Health. 2021 Aug 28;49(1):68. doi: 10.1186/s41182-021-00358-4.**

Diabetes mellitus and HIV infection among active tuberculosis patients in

Northwest Ethiopia: health facility-based cross-sectional study.

Tulu B(1)(2), Amsalu E(3), Zenebe Y(4), Abebe M(3), Fetene Y(3), Agegn M(3),

Abate A(3), Ponpetch K(5), Bekana T(6)(7), Gumi B(6), Ameni G(6)(8).

Author information:

(1)Department of Medical Laboratory Sciences, Bahir Dar University, Bahir Dar,

Ethiopia. tulubegna@gmail.com.

(2)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, PO Box 1176,

Addis AbabaAddis Ababa, Ethiopia. tulubegna@gmail.com.

(3)Department of Pediatric Nursing, Bahir Dar University, Bahir Dar, Ethiopia.

(4)Department of Medical Laboratory Sciences, Bahir Dar University, Bahir Dar,

Ethiopia.

(5)Sirindhorn College of Public Health Trang, Faculty of Public Health and

Allied Health Sciences, Praboromarajchanok Institute, Ministry of Public Health,

Nonthaburi, Thailand.

(6)Aklilu Lemma Institute of Pathobiology, Addis Ababa University, PO Box 1176,

Addis AbabaAddis Ababa, Ethiopia.

(7)Department of Biomedical Sciences, Faculty of Public Health and Medical

Science, Mettu University, Mettu, Ethiopia.

(8)Department of Veterinary Medicine, College of Agriculture and Veterinary

Medicine, United Arab Emirates University, PO Box 15551, Al Ain, United Arab

Emirates.

**BACKGROUND:** The prevalence of diabetes mellitus (DM) is increasing globally and

its comorbidity with tuberculosis (TB) is re-emerging, especially in low- and

middle-income countries.

**OBJECTIVE:** The main aim of this study is to determine the prevalence of DM and

HIV infection and their associated risk factors among active tuberculosis

patients in Northwest Ethiopia.

**METHODS:** This hospital-based cross-sectional study was conducted between

February 1st and June 30th, 2017 among active TB patients in two hospitals of

Northwest Ethiopia. Two hundred and sixty-seven active TB cases aged 18 years or

older were screened for diabetes using fasting blood glucose (FBG) test.

Semi-structured questionnaires were used to collect demographic data, lifestyle

habits and clinical data. Identification of pre-diabetes or diabetes in TB

patients was achieved according to American Diabetes Association guidelines

(2016).

**RESULTS:** Prevalence of DM and TB comorbidity was 11.5% (95% confidence interval,

CI 7.8-15.2) compared to 24.9% (95% CI 20.1-30.1) for pre-diabetes. Prevalence

of HIV/TB co-infection was 21.9% (95% CI 16.7-26.8). Risk of DM was higher in TB

patients from a rural location (adjusted odds ratio, aOR 3.13, 95% CI 1.02-9.62,

p = 0.046). Similarly, DM was higher in TB patients who have a family history of

DM (aOR 4.54, 95% CI 1.31-15.68, p = 0.017). Furthermore, HIV/TB co-infection

was identified as a predictor of DM comorbidity in active TB patients (aOR 5.11,

95% CI 2.01-12.98, p = 0.001).

**CONCLUSION:** The magnitude of DM and pre-diabetes in active TB patients in

Northwest Ethiopia was high, warranting collaborative efforts to improve

screening and adopt better clinical management strategies for DM-TB comorbid

patients. Furthermore, being rural residents, family history of DM and HIV/TB

co-infection were found to associate with DM among TB patients, highlighting the

importance of the above-mentioned risk factors in the clinical management of

this comorbidity.

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PMID: 34454627

**47. FEBS J. 2021 Aug 28. doi: 10.1111/febs.16170. Online ahead of print.**

Epigenetic code during mycobacterial infections: Therapeutic implications for

Tuberculosis.

Fatima S(1), Kumari A(1), Agarwal M(2), Pahuja I(1), Yadav V(3), Dwivedi VP(1),

Bhaskar A(1).

Author information:

(1)Immunobiology Group, International Centre for Genetic Engineering and

Biotechnology, New Delhi, India.

(2)Department of Biosciences, Jamia Hamdard University, New Delhi, India.

(3)Department of Microbiology, Central University of Haryana, India.

Epigenetics involves changing the gene function without any change in the

sequence of the genes. In the case of tuberculosis (TB) infections, the bacilli,

Mycobacterium tuberculosis (M.tb) uses epigenetics as a tool to protect itself

from the host immune system. TB is a deadly disease-causing maximum death per

year due to a single infectious agent. In the case of TB, there is an urgent

need for novel host-directed therapies which can effectively target the survival

and long term persistence of the bacteria without developing drug resistance in

the bacterial strains while also reducing the duration and toxicity associated

with the mainstream anti-TB drugs. Recent studies have suggested that TB

infection has a significant effect on the host epigenome thereby manipulating

the host immune response in the favor of the pathogen. M.tb alters the

activation status of key genes involved in the immune response against TB to

promote its survival and subvert the antibacterial strategies of the host. These

changes are reversible and can be exploited to design very efficient

host-directed therapies to fight against TB. This review has been written with

the purpose of discussing the role of epigenetic changes in TB pathogenesis and

the therapeutic approaches involving epigenetics, which can be utilized for

targeting the pathogen.

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DOI: 10.1111/febs.16170

PMID: 34453865

**48. Lancet Infect Dis. 2021 Sep;21(9):e272-e280. doi: 10.1016/S1473-3099(21)00077-3.**

Barriers and enablers to implementing tuberculosis control strategies in EU and

European Economic Area countries: a systematic review.

Conroy O(1), Wurie F(2), Collin SM(2), Edmunds M(2), de Vries G(3), Lönnroth

K(4), Abubakar I(5), Anderson SR(2), Zenner D(6).

Author information:

(1)TB Unit, National Infection Service, Public Health England, London, UK.

Electronic address: olivia.conroy@PHE.gov.uk.

(2)TB Unit, National Infection Service, Public Health England, London, UK.

(3)KNCV Tuberculosis Foundation, The Hague, Netherlands.

(4)Department of Public Health Sciences, Karolinska Institute, Stockholm,

Sweden.

(5)Institute for Global Health, University College London, London, UK.

(6)TB Unit, National Infection Service, Public Health England, London, UK;

Institute for Global Health, University College London, London, UK.

Meeting the 2035 WHO targets of reducing tuberculosis incidence by 90% from 2015

levels requires the implementation of country-specific tuberculosis control

strategies. This systematic review aims to identify factors that facilitate or

impede the implementation of such strategies in EU and European Economic Area

(EEA) settings. Focusing on providers of care, health system constraints, and

social and political factors, this Review complements available evidence on the

accessibility of tuberculosis services to recipients of care. Databases were

searched for EU and EEA articles published between Jan 1, 1997, and Nov 6, 2020,

that presented empirical data on tuberculosis policies, strategies, guidelines,

or interventions. 2061 articles were screened and 65 were included. The most

common barrier to tuberculosis control strategies described the divergence of

health-care practices from guidelines, often related to inadequate knowledge or

perceived usefulness of the guidelines by clinicians. The most commonly

identified enabler to tuberculosis control strategies was the documented

positive attitudes of health-care workers towards tuberculosis programmes.

Divergence between clinical practice and guidelines was described in most EU and

EEA settings, indicating the need for a focused review of guideline adherence.

Strengths of this study involve its broad inclusion criteria and wide range of

tuberculosis control strategies analysed.

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**49. Lancet Digit Health. 2021 Sep;3(9):e543-e554. doi:**

**10.1016/S2589-7500(21)00116-3.**

Tuberculosis detection from chest x-rays for triaging in a high

tuberculosis-burden setting: an evaluation of five artificial intelligence

algorithms.

Qin ZZ(1), Ahmed S(2), Sarker MS(2), Paul K(2), Adel ASS(2), Naheyan T(3),

Barrett R(3), Banu S(2), Creswell J(3).

Author information:

(1)Stop TB Partnership, Geneva, Switzerland. Electronic address:

zhizhenq@stoptb.org.

(2)International Centre for Diarrhoeal Disease Research, Bangladesh (icddr,b),

Dhaka, Bangladesh.

(3)Stop TB Partnership, Geneva, Switzerland.

Comment in

 Lancet Digit Health. 2021 Sep;3(9):e535-e536.

**BACKGROUND:** Artificial intelligence (AI) algorithms can be trained to recognise

tuberculosis-related abnormalities on chest radiographs. Various AI algorithms

are available commercially, yet there is little impartial evidence on how their

performance compares with each other and with radiologists. We aimed to evaluate

five commercial AI algorithms for triaging tuberculosis using a large dataset

that had not previously been used to train any AI algorithms.

**METHODS:** Individuals aged 15 years or older presenting or referred to three

tuberculosis screening centres in Dhaka, Bangladesh, between May 15, 2014, and

Oct 4, 2016, were recruited consecutively. Every participant was verbally

screened for symptoms and received a digital posterior-anterior chest x-ray and

an Xpert MTB/RIF (Xpert) test. All chest x-rays were read independently by a

group of three registered radiologists and five commercial AI algorithms: CAD4TB

(version 7), InferRead DR (version 2), Lunit INSIGHT CXR (version 4.9.0), JF

CXR-1 (version 2), and qXR (version 3). We compared the performance of the AI

algorithms with each other, with the radiologists, and with the WHO's Target

Product Profile (TPP) of triage tests (≥90% sensitivity and ≥70% specificity).

We used a new evaluation framework that simultaneously evaluates sensitivity,

proportion of Xpert tests avoided, and number needed to test to inform

implementers' choice of software and selection of threshold abnormality scores.

**FINDINGS:** Chest x-rays from 23 954 individuals were included in the analysis.

All five AI algorithms significantly outperformed the radiologists. The areas

under the receiver operating characteristic curve were 90·81% (95% CI

90·33-91·29) for qXR, 90·34% (89·81-90·87) for CAD4TB, 88·61% (88·03-89·20) for Lunit INSIGHT CXR, 84·90% (84·27-85·54) for InferRead DR, and 84·89%

(84·26-85·53) for JF CXR-1. Only qXR (74·3% specificity [95% CI 73·3-74·9]) and

CAD4TB (72·9% specificity [72·3-73·5]) met the TPP at 90% sensitivity. All five

AI algorithms reduced the number of Xpert tests required by 50% while

maintaining a sensitivity above 90%. All AI algorithms performed worse among

older age groups (>60 years) and people with a history of tuberculosis.

**INTERPRETATION:** AI algorithms can be highly accurate and useful triage tools for

tuberculosis detection in high-burden regions, and outperform human readers.

FUNDING: Government of Canada.

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**50. Lancet Digit Health. 2021 Sep;3(9):e535-e536. doi:**

**10.1016/S2589-7500(21)00142-4.**

Can AI technologies close the diagnostic gap in tuberculosis?

Tzelios C(1), Nathavitharana RR(2).

Author information:

(1)Harvard Medical School, Boston, MA, USA.

(2)Division of Infectious Diseases, Beth Israel Deaconess Medical Center and

Harvard Medical School, Boston, MA 02215, USA. Electronic address:

rnathavi@bidmc.harvard.edu.

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**51. Retina. 2021 Sep 1;41(9):e51-e52. doi: 10.1097/IAE.0000000000003268.**

Coffee Bean-Like Hemorrhages in Tuberculosis Associated Multifocal Choroiditis.

Patel A(1), Pathengay A, Panchal B.

Author information:

(1)Department of Retina and Vitreous, LV Prasad Eye Institute, GMR Varalakshmi

Campus, Visakhapatnam, India.

DOI: 10.1097/IAE.0000000000003268

PMID: 34432747

**52. Respirol Case Rep. 2021 Aug 17;9(9):e0830. doi: 10.1002/rcr2.830. eCollection**

**2021 Sep.**

A case of epithelioid cell granulomas arising at the margin of lung resection,

with high accumulation on 18F-fluorodeoxyglucose-positron emission tomography.

Yokotsuka S(1), Uematsu S(2), Okada M(2), Takamiya S(2), Ohashi S(2), Tanaka

Y(2), Suzuki K(2), Kitami A(2), Nemoto T(3).

Author information:

(1)Department of Medicine Showa University School of Medicine Tokyo Japan.

(2)Respiratory Disease Center Showa University Northern Yokohama Hospital

Yokohama Japan.

(3)Pathology and Laboratory Medicine Showa University Northern Yokohama Hospital

Yokohama Japan.

It is important to distinguish tumour recurrence from other conditions that

could show high accumulation on 18F-fluorodeoxyglucose-positron emission

tomography (FDG-PET). We describe the case of a 78-year-old woman who underwent

partial resection of the left lower lung lobe for carcinoid treatment 20 years

previously. Five years earlier, chest radiography revealed an abnormal shadow,

and chest computed tomography (CT) showed partial atelectasis in the left S8.

Periodical CT showed that the atelectasis had developed into a mass. The patient

was referred to our hospital. A mass of 45 mm diameter was detected on CT and it

had a maximum standardized uptake value of 8.91 on FDG-PET. We suspected

recurrence and performed surgery. Pathological examination revealed epithelioid

cell granuloma (maximum diameter, 25 mm) with necrosis. Tissue culture showed no

evidence of Mycobacterium tuberculosis. However, serum anti-MAC antibody level

was elevated, suggesting epithelioid cell granuloma caused by non-tuberculous

Mycobacterium infection.

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Australia, Ltd on behalf of The Asian Pacific Society of Respirology.

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**53. Proc Natl Acad Sci U S A. 2021 Aug 31;118(35):e2105800118. doi:**

**10.1073/pnas.2105800118.**

Phosphoenolpyruvate depletion mediates both growth arrest and drug tolerance of

Mycobacterium tuberculosis in hypoxia.

Lim J(1), Lee JJ(1), Lee SK(2), Kim S(1), Eum SY(2), Eoh H(3).

Author information:

(1)Department of Molecular Microbiology and Immunology, Keck School of Medicine,

University of Southern California, Los Angeles, CA 90033.

(2)Division of Immunology and Cellular Immunology, International Tuberculosis

Research Center, Changwon 51755, Republic of Korea.

(3)Department of Molecular Microbiology and Immunology, Keck School of Medicine,

University of Southern California, Los Angeles, CA 90033; heoh@usc.edu.

Mycobacterium tuberculosis (Mtb) infection is difficult to treat because Mtb

spends the majority of its life cycle in a nonreplicating (NR) state. Since NR

Mtb is highly tolerant to antibiotic effects and can mutate to become drug

resistant (DR), our conventional tuberculosis (TB) treatment is not effective.

Thus, a novel strategy to kill NR Mtb is required. Accumulating evidence has

shown that repetitive exposure to sublethal doses of antibiotics enhances the

level of drug tolerance, implying that NR Mtb is formed by adaptive metabolic

remodeling. As such, metabolic modulation strategies to block the metabolic

remodeling needed to form NR Mtb have emerged as new therapeutic options. Here,

we modeled in vitro NR Mtb using hypoxia, applied isotope metabolomics, and

revealed that phosphoenolpyruvate (PEP) is nearly completely depleted in NR Mtb.

This near loss of PEP reduces PEP-carbon flux toward multiple pathways essential

for replication and drug sensitivity. Inversely, supplementing with PEP restored

the carbon flux and the activities of the foregoing pathways, resulting in

growth and heightened drug susceptibility of NR Mtb, which ultimately prevented

the development of DR. Taken together, PEP depletion in NR Mtb is associated

with the acquisition of drug tolerance and subsequent emergence of DR,

demonstrating that PEP treatment is a possible metabolic modulation strategy to

resensitize NR Mtb to conventional TB treatment and prevent the emergence of DR.

DOI: 10.1073/pnas.2105800118

PMID: 34426499

**54. Rev Esp Med Nucl Imagen Mol (Engl Ed). 2021 Sep-Oct;40(5):315-317. doi:**

**10.1016/j.remnie.2020.09.007. Epub 2020 Dec 5.**

Unexpected concomitant parasitic infection and tuberculosis in the evaluation of

hypertrophic pachymeningitis with (18)F-FDG PET/CT: [[es]]Infección parasitaria

y tuberculosis como hallazgos inesperados en laevaluación de paquimeningitis

hipertrófica mediante (18)FDG-PET/TC.

Sanfiel Delgado A(1), Rodríguez-Alfonso B(2), Tibisay Vazquez Benitez G(3), Ruiz

Molina A(4), Mitjavila Casanovas M(1).

Author information:

(1)Departamento de Medicina Nuclear, Hospital Universitario Puerta de

Hierro-Majadahonda, Majadahonda, Madrid, Spain.

(2)Departamento de Medicina Nuclear, Hospital Universitario Puerta de

Hierro-Majadahonda, Majadahonda, Madrid, Spain. Electronic address:

brodrigueza@salud.madrid.org.

(3)Departamento de Patología, Hospital Universitario Puerta de

Hierro-Majadahonda, Majadahonda, Madrid, Spain.

(4)Departamento de Neurología, Hospital Universitario Puerta de

Hierro-Majadahonda, Majadahonda, Madrid, Spain.

DOI: 10.1016/j.remnie.2020.09.007

PMID: 34425973

**55. Lancet Glob Health. 2021 Sep;9(9):e1209. doi: 10.1016/S2214-109X(21)00306-5.**

Validating novel diagnostic assays for tuberculosis in the context of existing

tools.

Kerkhoff AD(1), Cattamanchi A(2), Muyoyeta M(3), Denkinger CM(4), Dowdy DW(5).

Author information:

(1)Division of HIV, Infectious Diseases and Global Medicine, Zuckerberg San

Francisco General Hospital and Trauma Center, University of California San

Francisco, San Francisco, CA 94110, USA. Electronic address:

andrew.kerkhoff@ucsf.edu.

(2)Center for Tuberculosis and Division of Pulmonary and Critical Care Medicine,

Zuckerberg San Francisco General Hospital and Trauma Center, University of

California San Francisco, San Francisco, CA 94110, USA; Uganda Tuberculosis

Implementation Research Consortium, Makerere University, Kampala, Uganda.

(3)TB Department, Centre for Infectious Disease Research in Zambia, Lusaka,

Zambia.

(4)Division of Tropical Medicine, Center of Infectious Diseases, University of

Heidelberg, Heidelberg, Germany.

(5)Uganda Tuberculosis Implementation Research Consortium, Makerere University,

Kampala, Uganda; Department of Epidemiology, Johns Hopkins Bloomberg School of

Public Health, Baltimore, MD, USA.

Comment on

 Lancet Glob Health. 2021 Jun;9(6):e841-e853.

DOI: 10.1016/S2214-109X(21)00306-5

PMID: 34416206 [Indexed for MEDLINE]

**56. FASEB J. 2021 Sep;35(9):e21853. doi: 10.1096/fj.202001581RR.**

Is Mycobacterium tuberculosis carcinogenic to humans?

Roy D(1), Ehtesham NZ(2), Hasnain SE(3)(4).

Author information:

(1)Department of Environmental Health Sciences, Florida International

University, Miami, FL, USA.

(2)ICMR-National Institute of Pathology, Safdarjung Hospital Campus, New Delhi,

India.

(3)Department of Life Sciences, School of Basic Sciences and Research, Sharda

University, Greater Noida, India.

(4)Department of Biochemical Engineering and Biotechnology, Indian Institute of

Technology, Delhi (IIT-D), New Delhi, India.

We highlight the ability of the tuberculosis (TB) causing bacterial pathogen,

Mycobacterium tuberculosis (Mtb), to induce key characteristics that are

associated with established IARC classified Group 1 and Group 2A carcinogenic

agents. There is sufficient evidence from epidemiological case-control, cohort

and meta-analysis studies of increased lung cancer (LC) risk in

pre-existing/active/old TB cases. Similar to carcinogens and other pathogenic

infectious agents, exposure to aerosol-containing Mtb sprays in mice produce

malignant transformation of cells that result in squamous cell carcinoma.

Convincing, mechanistic data show several characteristics shared between TB and

LC which include chronic inflammation, genomic instability and replicative

immortality, just to name a few cancer hallmarks. These hallmarks of cancer may

serve as precursors to malignant transformation. Together, these findings form

the basis of our postulate that Mtb is a complete human pulmonary carcinogen. We

also discuss how Mtb may act as both an initiating agent and promoter of tumor

growth. Forthcoming experimental studies will not only serve as proof-of-concept

but will also pivot our understanding of how to manage/treat TB cases as well as

offer solutions to clinical conundrums of TB lesions masquerading as tumors.

Clinical validation of our concept may also help pave the way for next

generation personalized medicine for the management of pulmonary TB/cancer

particularly for cases that are not responding well to conventional chemotherapy

or TB drugs.

© 2021 Federation of American Societies for Experimental Biology.

DOI: 10.1096/fj.202001581RR

PMID: 34416038

**57. Future Microbiol. 2021 Sep;16:935-948. doi: 10.2217/fmb-2021-0030. Epub 2021 Aug 20.**

Diagnosis of osteoarticular tuberculosis: multi-targeted loop-mediated

isothermal amplification assay versus multiplex PCR.

Khan A(1), Kamra E(1), Singh R(2), Sharma V(1)(3), Singh V(4), Mor P(1), Kaushik

S(1), Yadav A(5), Mehta PK(1).

Author information:

(1)Centre for Biotechnology, Maharshi Dayanand University, Rohtak, 124001,

India.

(2)Department of Orthopaedics, University of Health Sciences, Rohtak, 124001,

India.

(3)Department of Virology, Postgraduate Institute of Medical Education &

Research, Chandigarh, 160012, India.

(4)Department of Biostatistics, All India Institute of Medical Sciences, New

Delhi, 110021, India.

(5)Department of Microbiology, University of Health Sciences, Rohtak, 124001,

India.

**Aim:** Diagnosis of osteoarticular tuberculosis (OATB) is quite challenging and

there is an urgent need to design a prompt and precise diagnostic test. Methods:

We developed a multi-targeted loop-mediated isothermal amplification (LAMP)

assay using mpt64 (Rv1980c) and pstS1 (Rv0934) targets for the detection of

Mycobacterium tuberculosis in OATB patients. Results: The sensitivities of 100

and 82.4% were obtained in confirmed (n = 10) and suspected (n = 57) OATB cases,

respectively by multi-targeted LAMP with a specificity of 96.9% (n = 33).

Moreover, the sensitivities attained by multi-targeted LAMP in total OATB cases

were significantly higher (p < 0.05-0.01) than multiplex PCR (mpt64 + pstS1) and

GeneXpert assay. Conclusion: Our LAMP is simple, reliable and cost-effective

method, which may develop into an attractive diagnostic kit for early detection

of OATB cases.

Plain Language Summary: Lay abstract Diagnosis of osteoarticular tuberculosis

(OATB) or bone and joint TB caused by Mycobacterium tuberculosis (Mtb) is quite

difficult owing to the low bacterial load present in OATB specimens, and

difficulty of obtaining specimens since Mtb bacilli are only present deep inside

the tissues. Mostly, diagnosis of OATB relies on clinical findings and imaging,

which often mimic other pus-producing microbial infections and inflammatory

arthritis, while the conventional bacteriological tests (smear/culture) almost

fail. Therefore, we developed a multi-targeted loop-mediated isothermal

amplification (LAMP) assay for early detection of OATB cases, which showed

superiority over multiplex PCR and GeneXpert assay. Overall, our LAMP is

straightforward, accurate and low-cost assay that may lead to the development of

a diagnostic kit for routine use.

DOI: 10.2217/fmb-2021-0030

PMID: 34414775

**58. ERJ Open Res. 2021 Aug 31;7(3):00251-2021. doi: 10.1183/23120541.00251-2021.**

**eCollection 2021 Jul.**

Psychological stress and health-related quality of life among tuberculosis

patients: a prospective cohort study.

Febi AR(1), Manu MK(2), Mohapatra AK(1)(3), Praharaj SK(2), Guddattu V(3).

Author information:

(1)Dept of Respiratory Medicine, Kasturba Medical College, Manipal, Manipal

Academy of Higher Education, Manipal, Karnataka, India.

(2)Dept of Psychiatry, Kasturba Medical College, Manipal, Manipal, Manipal

Academy of Higher Education, Manipal, Karnataka, India.

(3)Dept of Data Science, Prasanna School of Public health, Manipal, Manipal

Academy of Higher Education, Manipal, Karnataka, India.

Economic, social and psychological distress is common in individuals affected by

tuberculosis (TB). However, the magnitude of distress, psychological

interventions and their effect on the treatment outcomes are often

under-evaluated. We examined the level of psychological stress and

health-related quality of life (HRQoL) of such patients and the effect of

antituberculosis therapy on them.  Our prospective cohort study included newly

diagnosed adult pulmonary and extrapulmonary TB patients. Assessment of

psychological stress was done using the seven-item Generalised Anxiety Disorder

questionnaire for anxiety and the nine-item Patient Health Questionnaire for

depression. HRQoL was assessed by using the WHOQOL-BREF questionnaire.  Of the

86 patients studied, 21 (24.4%) had anxiety symptoms at the baseline, which

reduced to 5.8% and 1.2% at 2 months and treatment completion, respectively

(p<0.001). Among the subjects, 18 (20.9%) patients had depression, which reduced

to 7% and 2.3% at 2 months and treatment completion, respectively (p<0.001). All

the mean domain scores of HRQoL were poor at the baseline, which showed

improvement at treatment completion (p<0.001).  Anxiety and depression were

common among TB patients, and there was significant progressive reduction during

and after treatment. TB had remarkable negative impacts on HRQoL, with the

physical domain being the most affected, and all the domain scores showed

significant improvement at treatment completion. Routine screening for

depression and anxiety and timely referral to a psychiatrist are required in TB

patients to improve the outcome of the disease and quality of life.

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PMCID: PMC8405877

PMID: 34476253

**59. Stem Cells Int. 2021 Aug 23;2021:9928379. doi: 10.1155/2021/9928379. eCollection 2021.**

Integration of Umbilical Cord Mesenchymal Stem Cell Application in

Hydroxyapatite-Based Scaffolds in the Treatment of Vertebral Bone Defect due to

Spondylitis Tuberculosis: A Translational Study.

Rahyussalim AJ(1)(2)(3), Nugroho A(1), Zufar MLL(1), Fathurrahman I(1),

Kurniawati T(2)(3).

Author information:

(1)Department of Orthopaedic & Traumatology, Cipto Mangunkusumo General

Hospital, Faculty of Medicine Universitas Indonesia, Jakarta, Indonesia.

(2)Stem Cell Medical Technology Integrated Service Unit, Cipto Mangunkusumo

General Hospital, Jakarta, Indonesia.

(3)Stem Cells and Tissue Engineering Research Cluster, Indonesian Medical

Education and Research Institute (IMERI), Faculty of Medicine Universitas

Indonesia, Jakarta, Indonesia.

**BACKGROUND:** Vertebral bone defect represents one of the most commonly found

skeletal problems in the spine. Progressive increase of vertebral involvement of

skeletal tuberculosis (TB) is reported as the main cause, especially in

developed countries. Conventional spinal fusion using bone graft has been

associated with donor-site morbidity and complications. We reported the

utilization of umbilical cord mesenchymal stem cells (UC-MSCs) combined with

hydroxyapatite (HA) based scaffolds in treating vertebral bone defect due to

spondylitis tuberculosis.

**MATERIALS AND METHODS:** Three patients with tuberculous spondylitis in the

thoracic, thoracolumbar, or lumbar region with vertebral body collapse of more

than 50 percent were included. The patient underwent a 2-stage surgical

procedure, consisting of debridement, decompression, and posterior stabilization

in the first stage followed by anterior fusion using the lumbotomy approach at

the second stage. Twenty million UC-MSCs combined with HA granules in 2 cc of

saline were transplanted to fill the vertebral bone defect. Postoperative

alkaline phosphatase level, quality of life, and radiological healing were

evaluated at one-month, three-month, and six-month follow-up.

**RESULTS:** The initial mean ALP level at one-month follow-up was 48.33 ± 8.50 U/L.

This value increased at the three-month follow-up but decreased at the six-month

follow-up time, 97 ± 8.19 U/L and 90.33 ± 4.16 U/L, respectively. Bone formation

of 50-75% of the defect site with minimal fracture line was found. Increased

bone formation comprising 75-100% of the total bone area was reported six months

postoperation. A total score of the SF-36 questionnaire showed better

progression in all 8 domains during the follow-up with the mean total score at

six months of 2912.5 ± 116.67 from all patients.

**CONCLUSION:** Umbilical cord mesenchymal stem cells combined with

hydroxyapatite-based scaffold utilization represent a prospective alternative

therapy for bone formation and regeneration of vertebral bone defect due to

spondylitis tuberculosis. Further clinical investigations are needed to evaluate

this new alternative.

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DOI: 10.1155/2021/9928379

PMCID: PMC8407992

PMID: 34475959

**60. J Assoc Physicians India. 2021 Aug;69(8):11-12.**

Peripheral Gangrene Associated with Disseminated Tuberculosis - a Rare

Manifestation.

Jacob AG(1), Koshy JM(2), Deodhar D(2), John M(3).

Author information:

(1)Post Graduate Resident, Department of Medicine, Christian Medical College,

Ludhiana, Punjab.

(2)Associate Professor, Department of Medicine, Christian Medical College,

Ludhiana, Punjab.

(3)Professor and Head, Department of Medicine, Christian Medical College,

Ludhiana, Punjab.

With global resurgence of M. tuberculosis infection, cases of extra pulmonary TB

have also shown an increase. Tuberculosis is a major cause of morbidity and

mortality in India. Although disseminated tuberculosis can affect most of the

organs, vasculitis presenting as peripheral gangrene as a manifestation of

tuberculosis is very rare. We report the case of a 70 years old male who

presented with gangrene of left leg complicating disseminated tuberculosis.

© Journal of the Association of Physicians of India 2011.

PMID: 34472816

**61. J Assoc Physicians India. 2021 Aug;69(8):11-12.**

Socio-psychological Effects on Tuberculosis Patients from Maharashtra, India.

Khairnar DR(1), Markad S(2).

Author information:

(1)Department of Sociology, Deogiri College, Aurangabad,

Maharashtra;Corresponding Author.

(2)Department of Sociology, Deogiri College, Aurangabad, Maharashtra.

**OBJECTIVES**: The purpose of this study was to identify the relationship between

socio-psychological factors and TB patients as well as to determine whether the

association differs from treated and untreated persons.

**METHODS**: This was a prospective study in a municipal corporation hospital in

Pune district. A total 104 patient sample were selected from the population;

criteria covered age group of 25 to 60 years along with their education and

economic background. Trained study nurses then collected baseline information

from consenting participants using a questionnaire.

**RESULTS:** After being cured from the disease, patients share clothes or utensils

with their family members. For a few patients psychological improvements were

observed after some period of treatment whereas as in majority of patients

psychological support by their family and friends was not received. This caused

increase in emotional stress despite patients got cured off the TB infection.

**CONCLUSION:** The important point noticed about the cured patients was augmented

fighting spirit against this deadly disease. Recovered patients want to live

more with the same joy and happiness after treatment.

© Journal of the Association of Physicians of India 2011.

PMID: 34472801

**62. Cureus. 2021 Jul 29;13(7):e16734. doi: 10.7759/cureus.16734. eCollection 2021**

**Jul.**

Pancreatic Tuberculosis: A Diagnostic Dilemma.

Haseeb S(1), Bilal MI(2), Bokhari SA(1), Mirza RT(3), Riyaz S(4).

Author information:

(1)Internal Medicine, Shifa International Hospital Islamabad, Islamabad, PAK.

(2)Medicine, Shifa College of Medicine, Islamabad, Islamabad, PAK.

(3)General surgery, Shifa International Hospital Islamabad, Islamabad, PAK.

(4)Gastroenterology, Shifa International Hospital Islamabad, Islamabad, PAK.

Despite the high prevalence of tuberculosis (TB) in developing countries,

pancreatic TB remains a rare disease. Pancreatic TB usually presents as fever,

night sweats, and abdominal pain in an immunocompromised individual. We present

a case of a patient with end-stage renal disease undergoing pre-transplant

workup who had an incidental finding of a pancreatic mass and necrotic

peri-pancreatic lymph nodes on a CT scan. The patient was diagnosed via

endoscopic ultrasound-guided biopsy as pancreatic TB. Anti-TB therapy was

started with positive results.

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DOI: 10.7759/cureus.16734

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PMID: 34471581

**63. Ther Adv Drug Saf. 2021 Aug 26;12:20420986211041277. doi:**

**10.1177/20420986211041277. eCollection 2021.**

Prediction of potential drug interactions between repurposed COVID-19 and

antitubercular drugs: an integrational approach of drug information software and

computational techniques data.

Thomas L(1), Birangal SR(2), Ray R(2), Sekhar Miraj S(1), Munisamy M(1), Varma

M(3), S V CS(4), Banerjee M(5), Shenoy GG(2), Rao M(6).

Author information:

(1)Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences,

Manipal Academy of Higher Education, Manipal, India.

(2)Department of Pharmaceutical Chemistry, Manipal College of Pharmaceutical

Sciences, Manipal Academy of Higher Education, Manipal, India.

(3)Department of Infectious Diseases, Kasturba Medical College, Manipal Academy

of Higher Education, Manipal, India.

(4)District Tuberculosis Control Office, Ajjarakad, Udupi, Karnataka, India.

(5)Department of Biochemistry, All India Institute of Medical Sciences, Jodhpur,

Rajasthan, India.

(6)Professor and Head, Department of Pharmacy Practice, Coordinator, Centre for

Translational Research, Manipal College of Pharmaceutical Sciences, Manipal

Academy of Higher Education (MAHE), Manipal 576104, Karnataka, India.

**INTRODUCTION:** Tuberculosis is a major respiratory disease globally with a higher

prevalence in Asian and African countries than rest of the world. With a larger

population of tuberculosis patients anticipated to be co-infected with COVID-19

infection, an ongoing pandemic, identifying, preventing and managing drug-drug

interactions is inevitable for maximizing patient benefits for the current

repurposed COVID-19 and antitubercular drugs.

**METHODS:** We assessed the potential drug-drug interactions between repurposed

COVID-19 drugs and antitubercular drugs using the drug interaction checker of

IBM Micromedex®. Extensive computational studies were performed at a molecular

level to validate and understand the drug-drug interactions found from the

Micromedex drug interaction checker database at a molecular level. The

integrated knowledge derived from Micromedex and computational data was collated

and curated for predicting potential drug-drug interactions between repurposed

COVID-19 and antitubercular drugs.

**RESULTS:** A total of 91 potential drug-drug interactions along with their

severity and level of documentation were identified from Micromedex between

repurposed COVID-19 drugs and antitubercular drugs. We identified 47

pharmacodynamic, 42 pharmacokinetic and 2 unknown DDIs. The majority of our

molecular modelling results were in line with drug-drug interaction data

obtained from the drug information software. QT prolongation was identified as

the most common type of pharmacodynamic drug-drug interaction, whereas drug-drug

interactions associated with cytochrome P450 3A4 (CYP3A4) and P-glycoprotein

(P-gp) inhibition and induction were identified as the frequent pharmacokinetic

drug-drug interactions. The results suggest antitubercular drugs, particularly

rifampin and second-line agents, warrant high alert and monitoring while

prescribing with the repurposed COVID-19 drugs.

**CONCLUSION:** Predicting these potential drug-drug interactions, particularly

related to CYP3A4, P-gp and the human Ether-à-go-go-Related Gene proteins, could

be used in clinical settings for screening and management of drug-drug

interactions for delivering safer chemotherapeutic tuberculosis and COVID-19

care. The current study provides an initial propulsion for further well-designed

pharmacokinetic-pharmacodynamic-based drug-drug interaction studies.

**PLAIN LANGUAGE SUMMARY:** Introduction:: Tuberculosis is a major respiratory

disease globally with a higher prevalence in Asian and African countries than

rest of the world. With a larger population of tuberculosis patients predicted

to be infected with COVID-19 during this period, there is a higher risk for the

occurrence of medication interactions between the medicines used for COVID-19

and tuberculosis. Hence, identifying and managing these interactions is vital to

ensure the safety of patients undergoing COVID-19 and tuberculosis treatment

simultaneously.Methods:: We studied the major medication interactions that could

likely happen between the various medicines that are currently given for

COVID-19 and tuberculosis treatment using the medication interaction checker of

a drug information software (Micromedex®). In addition, thorough molecular

modelling was done to confirm and understand the interactions found from the

medication interaction checker database using specific docking software.

Molecular docking is a method that predicts the preferred orientation of one

medicine molecule to a second molecule, when bound to each other to form a

stable complex. Knowledge of the preferred orientation may be used to determine

the strength of association or binding affinity between two medicines using

scoring functions to determine the extent of the interactions between medicines.

The combined knowledge from Micromedex and molecular modelling data was used to

properly predict the potential medicine interactions between currently used

COVID-19 and antitubercular medicines.Results:: We found a total of 91

medication interactions from Micromedex. Majority of our molecular modelling

findings matched with the interaction information obtained from the drug

information software. QT prolongation, an abnormal heartbeat, was identified as

one of the most common interactions. Our findings suggest that antitubercular

medicines, mainly rifampin and second-line agents, suggest high alert and

scrutiny while prescribing with the repurposed COVID-19 medicines.Conclusion::

Our current study highlights the need for further well-designed studies

confirming the current information for recommending safe prescribing in patients

with both infections.

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PMID: 34471515

**64. Cell Immunol. 2021 Aug 24;369:104426. doi: 10.1016/j.cellimm.2021.104426. Online ahead of print.**

Evaluation of autophagy mediators in myeloid-derived suppressor cells during

human tuberculosis.

Kotze LA(1), Leukes VN(1), Fang Z(1), Lutz MB(2), Fitzgerald BL(3), Belisle

J(3), Loxton AG(1), Walzl G(1), du Plessis N(4).

Author information:

(1)DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, South

African Medical Research Council for Tuberculosis Research, Division of

Molecular Biology and Human Genetics, Faculty of Medical and Health Sciences,

Stellenbosch University, Cape Town, South Africa.

(2)Institute of Virology and Immunobiology, University of Würzburg, Würzburg,

Germany.

(3)Department of Microbiology, Immunology and Pathology, Colorado State

University, Fort Collins, USA.

(4)DSI-NRF Centre of Excellence for Biomedical Tuberculosis Research, South

African Medical Research Council for Tuberculosis Research, Division of

Molecular Biology and Human Genetics, Faculty of Medical and Health Sciences,

Stellenbosch University, Cape Town, South Africa. Electronic address:

nelita@sun.ac.za.

Myeloid-derived suppressor cells (MDSC) are induced during active TB disease to

restore immune homeostasis but instead exacerbate disease outcome due to chronic

inflammation. Autophagy, in conventional phagocytes, ensures successful

clearance of M.tb. However, autophagy has been demonstrated to induce prolonged

MDSC survival. Here we investigate the relationship between autophagy mediators

and MDSC in the context of active TB disease and during anti-TB therapy. We

demonstrate a significant increase in MDSC frequencies in untreated active TB

cases with these MDSC expressing TLR4 and significantly more mTOR and IL-6 than

healthy controls, with mTOR levels decreasing during anti-TB therapy. Finally,

we show that HMGB1 serum concentrations decrease in parallel with mTOR. These

findings suggest a complex interplay between MDSC and autophagic mediators,

potentially dependent on cellular localisation and M.tb infection state.

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**Online ahead of print.**

Systematic measurement of combination-drug landscapes to predict in vivo

treatment outcomes for tuberculosis.

Larkins-Ford J(1), Greenstein T(2), Van N(3), Degefu YN(4), Olson MC(3), Sokolov

A(5), Aldridge BB(6).

Author information:

(1)Department of Molecular Biology and Microbiology, Tufts University School of

Medicine, Boston, MA 02111, USA; Stuart B. Levy Center for Integrated Management

of Antimicrobial Resistance, Boston, MA 02111, USA; Graduate School of

Biomedical Sciences, Tufts University School of Medicine, Boston, MA 02111, USA;

Laboratory of Systems Pharmacology, Harvard Program in Therapeutic Science,

Harvard Medical School, Boston, MA 02115, USA.

(2)Department of Molecular Biology and Microbiology, Tufts University School of

Medicine, Boston, MA 02111, USA; Stuart B. Levy Center for Integrated Management

of Antimicrobial Resistance, Boston, MA 02111, USA; Graduate School of

Biomedical Sciences, Tufts University School of Medicine, Boston, MA 02111, USA.

(3)Department of Molecular Biology and Microbiology, Tufts University School of

Medicine, Boston, MA 02111, USA.

(4)Department of Molecular Biology and Microbiology, Tufts University School of

Medicine, Boston, MA 02111, USA; Laboratory of Systems Pharmacology, Harvard

Program in Therapeutic Science, Harvard Medical School, Boston, MA 02115, USA.

(5)Laboratory of Systems Pharmacology, Harvard Program in Therapeutic Science,

Harvard Medical School, Boston, MA 02115, USA.

(6)Department of Molecular Biology and Microbiology, Tufts University School of

Medicine, Boston, MA 02111, USA; Stuart B. Levy Center for Integrated Management

of Antimicrobial Resistance, Boston, MA 02111, USA; Graduate School of

Biomedical Sciences, Tufts University School of Medicine, Boston, MA 02111, USA;

Laboratory of Systems Pharmacology, Harvard Program in Therapeutic Science,

Harvard Medical School, Boston, MA 02115, USA; Department of Biomedical

Engineering, Tufts University School of Engineering, Medford, MA 02155, USA.

Electronic address: bree.aldridge@tufts.edu.

Lengthy multidrug chemotherapy is required to achieve a durable cure in

tuberculosis. However, we lack well-validated, high-throughput in vitro models

that predict animal outcomes. Here, we provide an extensible approach to

rationally prioritize combination therapies for testing in in vivo mouse models

of tuberculosis. We systematically measured Mycobacterium tuberculosis response

to all two- and three-drug combinations among ten antibiotics in eight

conditions that reproduce lesion microenvironments, resulting in >500,000

measurements. Using these in vitro data, we developed classifiers predictive of

multidrug treatment outcome in a mouse model of disease relapse and identified

ensembles of in vitro models that best describe in vivo treatment outcomes. We

identified signatures of potencies and drug interactions in specific in vitro

models that distinguish whether drug combinations are better than the standard

of care in two important preclinical mouse models. Our framework is

generalizable to other difficult-to-treat diseases requiring combination

therapies. A record of this paper's transparent peer review process is included

in the supplemental information.

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PMID: 34469743

**66. Cell Rep Med. 2021 Aug 17;2(8):100372. doi: 10.1016/j.xcrm.2021.100372.**

**eCollection 2021 Aug 17.**

A recombinant bovine adenoviral mucosal vaccine expressing mycobacterial

antigen-85B generates robust protection against tuberculosis in mice.

Khan A(1), Sayedahmed EE(2), Singh VK(1), Mishra A(1), Dorta-Estremera S(3),

Nookala S(3), Canaday DH(4), Chen M(5), Wang J(6), Sastry KJ(3), Mittal SK(2),

Jagannath C(1).

Author information:

(1)Department of Pathology and Genomic Medicine, Houston Methodist Academic

Institute, Houston Methodist Research Institute & Weill Cornell Medical College,

Houston, TX, USA.

(2)Department of Comparative Pathobiology and Purdue Institute of Inflammation,

Immunology, and Infectious Disease, College of Veterinary Medicine, Purdue

University, West Lafayette, IN, USA.

(3)Department of Thoracic Head and Neck Medical Oncology, MD Anderson Cancer

Center, Houston, TX, USA.

(4)Department of Medicine, Case Western Reserve University and Cleveland

Veterans Affairs, Cleveland, OH, USA.

(5)Department of Pathology and Immunology, Baylor College of Medicine, Houston,

TX, USA.

(6)Immunobiology and Transplant Science Center, Houston Methodist Research

Institute, and Department of Surgery, Weill Cornell Medical College, Houston,

TX, USA.

Although the BCG vaccine offers partial protection, tuberculosis remains a

leading cause of infectious disease death, killing ∼1.5 million people annually.

We developed mucosal vaccines expressing the autophagy-inducing peptide C5 and

mycobacterial Ag85B-p25 epitope using replication-defective human adenovirus

(HAdv85C5) and bovine adenovirus (BAdv85C5) vectors. BAdv85C5-infected dendritic

cells (DCs) expressed a robust transcriptome of genes regulating antigen

processing compared to HAdv85C5-infected DCs. BAdv85C5-infected DCs showed

enhanced galectin-3/8 and autophagy-dependent in vitro Ag85B-p25 epitope

presentation to CD4 T cells. BCG-vaccinated mice were intranasally boosted using

HAdv85C5 or BAdv85C5 followed by infection using aerosolized Mycobacterium

tuberculosis (Mtb). BAdv85C5 protected mice against tuberculosis both as a

booster after BCG vaccine (>1.4-log10 reduction in Mtb lung burden) and as a

single intranasal dose (>0.5-log10 reduction). Protection was associated with

robust CD4 and CD8 effector (TEM), central memory (TCM), and CD103+/CD69+

lung-resident memory (TRM) T cell expansion, revealing BAdv85C5 as a promising

mucosal vaccine for tuberculosis.

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**67. Gynecol Oncol Rep. 2021 Aug 14;37:100848. doi: 10.1016/j.gore.2021.100848.**

**eCollection 2021 Aug.**

Co-existent abdominoperitoneal tuberculosis with endometrial cancer: A

diagnostic and surgical challenge.

Ashraf M(1), Goh WA(2), Tan EMX(2), Nadarajah R(2).

Author information:

(1)Department of Obstetrics and Gynaecology, SingHealth, Singapore.

(2)Yong Loo Lin School of Medicine, National University of Singapore, Singapore.

The presence of abdominoperitoneal tuberculosis (APTB) complicates the

diagnosis, staging and management of endometrial cancer. Lymph node involvement

in APTB may mimic metastatic lymphadenopathy in patients with endometrial

cancer. To our knowledge, there have only been 2 previous case reports on this

topic. We will describe 3 cases of endometrial cancer co-existing with APTB. The

1st case is a 57-year-old female who underwent elective total laparoscopic

hysterectomy with bilateral salpingo-oophorectomy (TLHBSO) and bilateral pelvic

lymph node dissection (PLND). The final diagnosis is Stage 3C1 endometrial

endometroid carcinoma with mucinous differentiation. The 2nd case is a

70-year-old female with who underwent total abdominal hysterectomy with

bilateral salpingo-oophorectomy (TAHBSO) and PLND. The final diagnosis is a

Stage 1A endometrioid adenocarcinoma. The 3rd case is a 63-year-old female who

underwent TAHBSO and PLND and the final diagnosis was a mixed high-grade serous

(90%) and endometrioid (10%) carcinoma of the endometrium. In these cases, the

importance of surgical staging is emphasised to accurately stage endometrial

cancer. Moreover, thorough peri-operative optimisations by a multi-disciplinary

team are essential to improve the outcomes of surgery.

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**68. Open Forum Infect Dis. 2021 Aug 1;8(8):ofab413. doi: 10.1093/ofid/ofab413.**

**eCollection 2021 Aug.**

QT Interval Prolongation in People Treated With Bedaquiline for Drug-Resistant

Tuberculosis Under Programmatic Conditions: A Retrospective Cohort Study.

Isralls S(1), Baisley K(1)(2), Ngam E(3), Grant AD(2)(4)(5)(6), Millard

J(2)(7)(8).

Author information:

(1)London School of Hygiene and Tropical Medicine, London, United Kingdom.

(2)Africa Health Research Institute, Durban, South Africa.

(3)University of KwaZulu-Natal, Durban, South Africa.

(4)Tuberculosis Centre, London School of Hygiene and Tropical Medicine, London,

United Kingdom.

(5)School of Laboratory Medicine and Medical Sciences, College of Health

Sciences, University of KwaZulu-Natal, Durban, South Africa.

(6)School of Public Health, University of the Witwatersrand, Johannesburg, South

Africa.

(7)Wellcome Trust Liverpool Glasgow Centre for Global Health Research,

Liverpool, United Kingdom.

(8)Institute of Infection and Global Health, University of Liverpool, Liverpool,

United Kingdom.

**BACKGROUND:** Bedaquiline has a black-box warning of the risk of arrhythmias and

sudden death. This study aimed to determine the incidence of QTc prolongation

and cardiac events in patients receiving bedaquiline for drug-resistant

tuberculosis (DR-TB) under programmatic conditions.

**METHODS:** Retrospective cohort study of patients receiving bedaquiline at a DR-TB

hospital in KwaZulu Natal, South Africa from September 2017 to February 2019.

The primary outcome, a prolonged QT interval corrected using the Fridericia

formula (QTcF), was defined as QTcF >500 ms, QTcF change >60 ms from baseline,

or both.

**RESULTS**: Among 420 patients (66.2% male, median age 36 years), the median QTcF

was 406.4 (interquartile range [IQR], 389.1-421.3) ms at baseline, increasing to

430.5 (IQR, 414.4-445.1) ms by 3 months and 434.0 (IQR, 419.0-447.9) ms at 6

months. Eighteen of 420 patients (4.3%) had a QTcF >500 ms and 110 of 420

patients (26.2%) had a QTcF change >60 ms. There were no recorded arrhythmias or

cardiac deaths. Odds of prolonged QTcF were increased with concomitant azoles

(adjusted odds ratio [aOR], 5.61 [95% confidence interval (CI), 2.26-13.91]; P <

.001) and an inverse association with HIV-positive status (aOR, 0.34 [95% CI,

.15-.75]; P = .008) and hypertension (aOR, 0.13 [95% CI, .02-.86]; P = .02).

After prolongation, the QTcF declined to <500 ms, whether drugs were interrupted

or not.

**CONCLUSIONS:** We observed a modest prolongation of QTcF, maximal at week 15;

there were no recorded arrhythmias or related deaths.

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Infectious Diseases Society of America.

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PMID: 34466629

**69. New Microbes New Infect. 2021 Aug 1;43:100921. doi: 10.1016/j.nmni.2021.100921.**

**eCollection 2021 Sep.**

Beijing genotype of Mycobacterium tuberculosis is associated with extensively

drug-resistant tuberculosis: A global analysis.

Keikha M(1)(2), Majidzadeh M(1)(2).

Author information:

(1)Antimicrobial Resistance Research Center, Mashhad University of Medical

Sciences, Mashhad, Iran.

(2)Department of Microbiology and Virology, Faculty of Medicine, Mashhad

University of Medical Sciences, Mashhad, Iran.

We found that the frequency of Beijing genotype among XDR-TB strains was high.

The data in this study would help guide the TB control program, and we however

need further investigation to confirm the reliability of the present findings.

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**70. Int J Prison Health. 2021 Aug 16;ahead-of-print(ahead-of-print). doi:**

**10.1108/IJPH-01-2021-0012.**

Pulmonary tuberculosis among prisoners in Southern Thailand: prevalence and its

association with imprisonment status.

Bilmumad B(1), Liabsuetrakul T(2), Ngamtrairai N(3), Chongsuvivatwong V(2).

Author information:

(1)Epidemiology Unit, Faculty of Medicine, Prince of Songkla University,

Songkhla, Thailand, and Songkhla Correctional Institution for Drug Addicts,

Department of Corrections Thailand, Mueang, Thailand.

(2)Epidemiology Unit, Faculty of Medicine, Prince of Songkla University,

Songkhla, Thailand.

(3)Songkhla Central Prison, Department of Corrections Thailand, Mueang,

Thailand.

**PURPOSE:** This study aims to measure the prevalence of pulmonary tuberculosis

(PTB), its association with imprisonment status and to document the treatment

success rate (TSR) among prisoners in Songkhla province, Southern Thailand.

**DESIGN/METHODOLOGY/APPROACH:** A retrospective cross-sectional study was conducted

in five prisons in Songkhla province, including all prisoners in the fiscal of

year 2019, who had an annual chest radiography (CXR) screening result.

Information of prisoners who had been imprisoned from 1 October 2018 to 30

September 2019, were reviewed for PTB diagnosis. Imprisonment status and other

associated factors with PTB were analyzed using multiple logistic regression.

**FINDINGS:** The prevalence of PTB was 2.72%. Prisoners having new or transfer-in

status were more likely to have PTB. Those aged 40-80 years, who had smoked for

ten years or more, or who were underweight, had higher odds of having PTB. TSR

among prisoners with PTB in this study was 94.9%.

**ORIGINALITY/VALUE:** The prevalence of PTB among prisoners having annual CXR

screening was high. Detection of PTB was higher among new or transfer-in

prisoners; therefore, the CXR for PTB screening before admission to prison

should be performed to prevent transmission to other prisoners.

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PMID: 34464526

**71. J Public Health Res. 2021 Aug 11;10(3). doi: 10.4081/jphr.2021.1896.**

Oral anti-tuberculosis drugs: An urgent medication reconciliation at hospitals

in Indonesia.

Herawati F(1), Fahmi EY(2), Pratiwi NA(3), Ramdani D(4), Jaelani AK(5), Yulia

R(6), Andrajati R(7).

Author information:

(1)Department of Clinical and Community Pharmacy, Faculty of Pharmacy,

University of Surabaya, Jalan Raya Kalirungkut, Surabaya; Department of

Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Indonesia,

Depok . fauna@staff.ubaya.ac.id.

(2)Department of Clinical and Community Pharmacy, Faculty of Pharmacy,

University of Surabaya, Jalan Raya Kalirungkut, Surabaya.

ekayuliantini11@gmail.com.

(3)Department of Clinical and Community Pharmacy, Faculty of Pharmacy,

University of Surabaya, Jalan Raya Kalirungkut, Surabaya.

nrauliapratiwi@gmail.com.

(4)Department of Pharmacy, RSU Haji, Surabaya. deramdani123@gmail.com.

(5)Department of Pharmacy, RSUD Bangil, Pasuruan. abusuquf@yahoo.co.id.

(6)Department of Clinical and Community Pharmacy, Faculty of Pharmacy,

University of Surabaya, Jalan Raya Kalirungkut, Surabaya.

rika\_y@staff.ubaya.ac.id.

(7)Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy,

Universitas Indonesia, Depok. retnosaria@gmail.com.

**BACKGROUND:** Four oral anti-tuberculosis drugs are conceived to be the most

effective ones to eradicate Mycobacterium tuberculosis bacteria and to obviate

the resistant organisms. However, the patients' adherence and medication

discrepancies are obstacles to achieving the goal. This study aimed to define

the anti-tuberculosis drugs used in the hospitals and to detect the

discrepancies in the continuity of the tuberculosis treatment.

**DESIGN AND METHODS:** This retrospective cross-sectional study was based on

medical records of adult patients, and was conducted in two district tertiary

care hospitals. Only 35 out of 136 patient records from Hospital A and 33 out of

85 records from Hospital B met the inclusion criteria.

**RESULTS:** The most common systemic anti-infective drugs in the study were

ceftriaxone (51.80 DDD/100 patient-days) used in Hospital A and isoniazid (59.53

DDD/100 patient-days) used in Hospital B. The number of rifampicin prescriptions

was less than that of isoniazid. Each patient received an average of two DDD/100

patient-days, which is an under dosage for an effective treatment.

**CONCLUSION:** This study showed a medication discrepancy of Tuberculosis therapy.

Tuberculosis patients' medical histories are not under the full attention of

treating physicians wherever they are admitted. Thus, medication reconciliation

is needed to accomplish the goal of a Tuberculosis-free world in 2050.

DOI: 10.4081/jphr.2021.1896

PMID: 34463088

**72. Antibodies (Basel). 2021 Aug 26;10(3):34. doi: 10.3390/antib10030034.**

Immunochemistry-Based Diagnosis of Extrapulmonary Tuberculosis: A Strategy for

Large-Scale Production of MPT64-Antibodies for Use in the MPT64 Antigen

Detection Test.

Hoel IM(1)(2)(3), Ali IAM(1), Ishtiaq S(4), Sviland L(3)(5), Wiker H(2), Mustafa

T(1)(6).

Author information:

(1)Centre for International Health, Department of Global Public Health and

Primary Care, University of Bergen, 5020 Bergen, Norway.

(2)Department of Clinical Science, University of Bergen, 5020 Bergen, Norway.

(3)Department of Clinical Medicine, University of Bergen, 5020 Bergen, Norway.

(4)Department of Histopathology, Gulab Devi Chest Hospital Lahore, Lahore 54000,

Pakistan.

(5)Department of Pathology, Haukeland University Hospital, 5021 Bergen, Norway.

(6)Department of Thoracic Medicine, Haukeland University Hospital, 5021 Bergen,

Norway.

Tuberculosis (TB) is a global health problem. The immunohistochemistry

(IHC)-based MPT64 antigen detection test has shown promising results for

diagnosing extrapulmonary TB in previous studies. However, the anti-MPT64

antibody currently used in the test is in limited supply, and reproduction of a

functional antibody is a prerequisite for further large-scale use. Various

antigen-adjuvant combinations and immunisation protocols were tested in mice and

rabbits to generate monoclonal and polyclonal antibodies. Antibodies were

screened in IHC, and the final new antibody was validated on clinical human

specimens. We were not able to generate monoclonal antibodies that were

functional in IHC, but we obtained multiple functional polyclonal antibodies

through careful selection of antigen-adjuvant and comprehensive screening in IHC

of both pre-immune sera and antisera. To overcome the limitation of

batch-to-batch variability with polyclonal antibodies, the best performing

individual polyclonal antibodies were pooled to one final large-volume new

anti-MPT64 antibody. The sensitivity of the new antibody was in the same range

as the reference antibody, while the specificity was somewhat reduced. Our

results suggest that it possible to reproduce a large-volume functional

polyclonal antibody with stable performance, thereby securing stable supplies

and reproducibility of the MPT64 test, albeit further validation remains to be

done.

DOI: 10.3390/antib10030034

PMCID: PMC8406093

PMID: 34462410

**73. Biosystems. 2021 Aug 27:104509. doi: 10.1016/j.biosystems.2021.104509. Online**

**ahead of print.**

Study of the bioenergetics to identify the novel pathways as a drug target

against Mycobacterium tuberculosis using Petri net.

Gupta S(1), Fatima Z(2), Kumawat S(3).

Author information:

(1)Department of Mathematics, Amity School of Applied Sciences, Amity University

Haryana, Gurugram, India.

(2)Amity Institute of Biotechnology, Amity University Haryana, Gurugram, India.

Electronic address: ksunita86@gmail.com.

(3)Department of Mathematics, Amity School of Applied Sciences, Amity University

Haryana, Gurugram, India. Electronic address: zfatima@ggn.amity.edu.

Tuberculosis is one of the life-threatening diseases globally, caused by the

bacteria Mycobacterium tuberculosis. In order to control this epidemic globally,

there is an urgent need to discover new drugs with novel mechanism of action

that can help in shortening the duration of treatment for both drug resistant

and drug sensitive tuberculosis. Mycobacterium essentially depends on oxidative

phosphorylation for its growth and establishment of pathogenesis. This pathway

is unique in Mycobacterium tuberculosis as compared to host due to the

differences in some of the enzyme complexes carrying electron transfer. Hence,

it serves as an important drug target area. The uncouplers which inhibit

adenosine triphosphate synthesis, could play a vital role in serving as

antimycobacterial agents and and thus could help in eradicating this deadly

disease. In this article, the bioenergetics of Mycobacterium tuberculosis are

studied with and without uncouplers using Petri net. Petri net is among the most

widely used mathematical and computational tools to model and study the complex

biochemical networks. We first represented the bioenergetic pathway as a Petri

net which is then validated and analyzed using invariant analysis techniques of

Petri net. The valid mathematical models presented here are capable to explain

the molecular mechanism of uncouplers and the processes occurring within the

electron transport chain of Mycobacterium tuberculosis. The results explained

the net behavior in agreement with the biological results and also suggested

some possible processes and pathways to be studied as a drug target for

developing antimycobacterials.

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An Automated Culture System for Use in Preclinical Testing of Host-Directed

Therapies for Tuberculosis.

O'Leary S(1), Bahlool AZ(2), O'Connor G(3), Cryan SA(4), Keane JM(1), O'Sullivan

MP(5).

Author information:

(1)Department of Clinical Medicine, Trinity Translational Medicine Institute,

St. James's Hospital, Trinity College Dublin, The University of Dublin.

(2)Department of Clinical Medicine, Trinity Translational Medicine Institute,

St. James's Hospital, Trinity College Dublin, The University of Dublin; School

of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in Ireland

(RCSI).

(3)School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in

Ireland (RCSI).

(4)School of Pharmacy and Biomolecular Sciences, Royal College of Surgeons in

Ireland (RCSI); SFI Advanced Materials and Bioengineering Research (AMBER)

Centre, RCSI & TCD; SFI Centre for Research in Medical Devices (CURAM), RCSI,

Dublin and National University of Ireland.

(5)Department of Clinical Medicine, Trinity Translational Medicine Institute,

St. James's Hospital, Trinity College Dublin, The University of Dublin;

mary.osullivan@tcd.ie.

Mycobacterium tuberculosis (Mtb), the causative agent of tuberculosis (TB), was

the most significant infectious disease killer globally until the advent of

COVID-19. Mtb has evolved to persist in its intracellular environment, evade

host defenses, and has developed resistance to many anti-tubercular drugs. One

approach to solving resistance is identifying existing approved drugs that will

boost the host immune response to Mtb. These drugs could then be repurposed as

adjunctive host-directed therapies (HDT) to shorten treatment time and help

overcome antibiotic resistance. Quantification of intracellular Mtb growth in

macrophages is a crucial aspect of assessing potential HDT. The gold standard

for measuring Mtb growth is counting colony-forming units (CFU) on agar plates.

This is a slow, labor-intensive assay that does not lend itself to rapid

screening of drugs. In this protocol, an automated, broth-based culture system,

which is more commonly used to detect Mtb in clinical specimens, has been

adapted for preclinical screening of host-directed therapies. The capacity of

the liquid culture assay system to investigate intracellular Mtb growth in

macrophages treated with HDT was evaluated. The HDTs tested for their ability to

inhibit Mtb growth were all-trans Retinoic acid (AtRA), both in solution and

encapsulated in poly(lactic-co-glycolic acid) (PLGA) microparticles and the

combination of interferon-gamma and linezolid. The advantages of this automated

liquid culture-based technique over the CFU method include simplicity of setup,

less labor-intensive preparation, and faster time to results (5-12 days compared

to 21 days or more for agar plates).

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**75. J Xray Sci Technol. 2021 Aug 26. doi: 10.3233/XST-210976. Online ahead of print.**

Tuberculosis detection in chest X-ray using Mayfly-algorithm optimized

dual-deep-learning features.

Rajakumar MP(1), Sonia R(2), Uma Maheswari B(1), Karuppiah SP(1).

Author information:

(1)St. Joseph's College of Engineering, OMR, Chennai, India.

(2)B.S Abdur Rahman Crescent Institute of Science & Technology, Chennai, India.

World-Health-Organization (WHO) has listed Tuberculosis (TB) as one among the

top 10 reasons for death and an early diagnosis will help to cure the patient by

giving suitable treatment. TB usually affects the lungs and an accurate

bio-imaging scheme will be apt to diagnose the infection. This research aims to

implement an automated scheme to detect TB infection in chest radiographs

(X-ray) using a chosen Deep-Learning (DL) approach. The primary objective of the

proposed scheme is to attain better classification accuracy while detecting TB

in X-ray images. The proposed scheme consists of the following phases namely,

(1) image collection and pre-processing, (2) feature extraction with pre-trained

VGG16 and VGG19, (3) Mayfly-algorithm (MA) based optimal feature selection, (4)

serial feature concatenation and (5) binary classification with a 5-fold cross

validation. In this work, the performance of the proposed DL scheme is

separately validated for (1) VGG16 with conventional features, (2) VGG19 with

conventional features, (3) VGG16 with optimal features, (4) VGG19 with optimal

features and (5) concatenated dual-deep-features (DDF). All experimental

investigations are conducted and achieved using MATLAB® program. Experimental

outcome confirms that the proposed system with DDF yields a classification

accuracy of 97.8%using a K Nearest-Neighbor (KNN) classifier.

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**76. Front Vet Sci. 2021 Aug 11;8:674636. doi: 10.3389/fvets.2021.674636. eCollection 2021.**

Evaluation of P22 ELISA for the Detection of Mycobacterium bovis-Specific

Antibody in the Oral Fluid of Goats.

Ortega J(1)(2), Infantes-Lorenzo JA(3), Bezos J(1)(2), Roy Á(1), de Juan

L(1)(2), Romero B(1), Moreno I(3), Gómez-Buendía A(1), Agulló-Ros I(4),

Domínguez L(1)(2), Domínguez M(3).

Author information:

(1)VISAVET Health Surveillance Centre, Complutense University of Madrid, Madrid,

Spain.

(2)Departamento de Sanidad Animal, Facultad de Veterinaria, Universidad

Complutense de Madrid, Madrid, Spain.

(3)Unidad de Inmunología Microbiana, Centro Nacional de Microbiología, Instituto

de Investigación Carlos III, Madrid, Spain.

(4)Grupo de Investigación en Sanidad Animal y Zoonosis, Departamento de Anatomía

y Anatomía Patológica Comparadas, Facultad de Veterinaria, Universidad de

Córdoba, Córdoba, Spain.

The ante-mortem diagnosis of tuberculosis (TB) in ruminants is based mainly on

the intradermal tuberculin test and the IFN-γ assay. Antibody (Ab)-based tests

have emerged as potential tools for the detection of TB infected animals using

serum, plasma, or even milk samples. Oral fluids have also been evaluated as

alternative samples with which to detect specific Abs against Mycobacterium

bovis in pigs or wild boars, but not in ruminants. The objective of this study

was, therefore, to evaluate the performance of an in house-ELISA for TB

diagnosis (P22 ELISA) in goats as an experimental model for the diagnosis of TB

using oral fluid samples. Oral fluid samples from 64 goats from a TB-infected

herd (n = 197) and all the animals from a TB-free herd (n = 113) were analyzed

using the P22 ELISA. The estimated sensitivity (Se) and specificity (Sp) were

34.4% (95% CI: 22.4-45.6) and 100% (95% CI: 97.4-100), respectively. The optimal

cut-off point was set at 100% according to the ROC analysis. Those animals with

a higher level of Abs in their oral fluid attained a higher lesion score (p =

0.018). In fact, when taking into account only the setting of the animals with

severe lesions (n = 16), the ELISA showed a Se of 75% (95% CI: 53.7-96.2).

Results of the present study suggest that the P22 ELISA is highly specific but

has a limited value detecting infected animals in oral fluid samples.

Nevertheless, its performance is significantly higher in the presence of severe

lesions.

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Gómez-Buendía, Agulló-Ros, Domínguez and Domínguez.

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**Online ahead of print.**

Clinical course of peritoneal dialysis-related peritonitis due to

non-tuberculosis mycobacterium - A single centre experience spanning 20 years.

Fung WW(1), Chow KM(1), Li PK(1), Szeto CC(1)(2).

Author information:

(1)Department of Medicine and Therapeutics, Prince of Wales Hospital, The

Chinese University of Hong Kong, Shatin, Hong Kong, China.

(2)Li Ka Shing Institute of Health Sciences (LiHS), The Chinese University of

Hong Kong, Shatin, Hong Kong, China.

**BACKGROUND:** Peritoneal dialysis (PD)-related peritonitis caused by

non-tuberculous mycobacteria (NTM) are difficult to diagnose, is associated with

significant morbidity and mortality, and clinical course remains unclear. We

determined the prevalence and clinical course of peritonitis caused by these

organisms through our kidney registry over 20-year period.

**METHOD:** We reviewed all patients with NTM peritonitis identified in our tertiary

centre between July 2000 and July 2020. The demographic characteristics,

microbiological and clinical outcomes were examined.

**RESULT:** Among 27 patients identified, 20 patients presented with abdominal pain

and all had cloudy peritoneal fluid. Twenty-one cases had concomitant exit site

infection and 14 cases had prior antibiotic use. The majority of the cases are

caused by Mycobacterium chelonae (37%) and Mycobacterium fortuitum (29.7%), with

most being resistant to fluoroquinolones (59.3%) and cefoxitin (73.1%). They are

all sensitive to amikacin otherwise. None of the cases achieve primary response

at day 10 and 20 cases resulted in Tenckhoff catheter removal. Only two of them

were able to resume PD. Eight patients died in our cohort. The presence of exit

site infection, the use of prior antibiotics and topical disinfectants did not

associate with a poorer outcome.

**CONCLUSION:** NTM peritonitis remains difficult to treat and often with a delay in

diagnosis. Refractory peritonitis with negative culture and a poor response to

standard antibiotics should raise a possibility of NTM infection and prompt

catheter removal and an expert with experience treating NTM infections should be

consulted.

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Accelerated progression of pulmonary tuberculosis in a COVID-19 patient after

corticosteroid treatment.

Liu WD(1), Wang JT(2), Hung CC(3), Chang SC(4).

Author information:

(1)Department of Internal Medicine, National Taiwan University Hospital and

National Taiwan University College of Medicine, Taipei, Taiwan; Department of

Medicine, National Taiwan University Cancer Center, Taipei, Taiwan. Electronic

address: b95401043@ntu.edu.tw.

(2)Department of Internal Medicine, National Taiwan University Hospital and

National Taiwan University College of Medicine, Taipei, Taiwan. Electronic

address: wang.jt1968@gmail.com.

(3)Department of Internal Medicine, National Taiwan University Hospital and

National Taiwan University College of Medicine, Taipei, Taiwan; Department of

Tropical Medicine and Parasitology, National Taiwan University College of

Medicine, Taipei, Taiwan; Department of Medical Research, China Medical

University Hospital, Taichung, Taiwan; China Medical University, Taichung,

Taiwan. Electronic address: hcc0401@ntu.edu.tw.

(4)Department of Internal Medicine, National Taiwan University Hospital and

National Taiwan University College of Medicine, Taipei, Taiwan. Electronic

address: changsc@ntu.edu.tw.

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Imaging diagnosis of sternal tuberculosis- A report of two cases of the ancient

disease with a new demeanour.

Grover DSB(1), Rai DV(1), Grover DH(2), Kumar DD(1), Kundra DR(1), Gautam

DVK(3), Devra DAG(4).

Author information:

(1)Department of Radiology and Imaging, School of Medical Sciences and Research,

Sharda Hospital, Sharda University, Greater Noida, 201306, Uttar Pradesh, India.

(2)Department of Radiology & Imaging, Ichan School of Medicine at Mount Sinai

West, New York.

(3)Department of Orthopedic Surgery, School of Medical Sciences and Research,

Sharda Hospital, Sharda University, Greater Noida, 201306, Uttar Pradesh, India.

(4)Department of Pathology, School of Medical Sciences and Research, Sharda

Hospital, Sharda University, Greater Noida, 201306, Uttar Pradesh, India.

Tuberculosis is an ancient disease known to have existed even in the Egyptian

civilization. It is estimated that a quarter of the world's population is

already infected and 1 million will die of the disease, in the current year.

Although tuberculosis may occur in any organ, extra- pulmonary tuberculosis

accounts for 10%-14% of all cases of tuberculosis. Skeletal involvement

comprises only 1 to 5 % of all types of tuberculosis and the most frequently

involved site in the skeleton is the vertebral column, amongst the skeletal

structures, the sternum is involved very rarely, accounting for just 1-2% of all

bone and joint tuberculosis. We report two cases of sternal tuberculosis,and

enumerate the imaging appearances seen at ultrasound, CT and MRI and also

highlight a relatively underemphasised complication of mediastinal involvement

due to a retrosternal abscess. Rapid diagnosis by imaging studies led to early

treatment and prevented catastrophic consequences of diffuse mediastinitis.

Awareness of tuberculosis and its atypical skeletal manifestations is important

not only in developing countries with endemic disease, but also in developed

countries, due to its resurgence by the HIV epidemic and also because extensive

international travel and transcontinental migration continues to facilitate

greater disease transmission.

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