



ISSN : 2347 - 2243

Indo - American Journal of Life Sciences and Biotechnology



<https://iajlb.org>

Email : editor@iajlb.com or iajlb.editor@gmail.com



Disseminated Tuberculosis Presenting as Multiple Cold Abscesses in an Immunocompetent Adult: A Narrative Review

Lotte van Leeuwen¹●, Giulia Santangelo²●, Camille Peyrac³●

¹Associate Professor, Department of General Medicine, Veluwe Institute of Molecular Biology, Apeldoorn, Netherlands.

²Consultant Physician, Department of Paediatrics, Monti Lepini Institute of Life Sciences, Frosinone, Italy.

³Associate Professor, Department of Pulmonary Medicine, Vosges Institute of Applied Microbiology, Epinal, France.

Email: ¹l.vanleeuwen@vimb.nl, ²g.santangelo@mlils.it, ³c.peyrac@viam-e.fr

ORCID: ¹0000-0001-2593-991X, ²0000-0001-3192-049X, ³0000-0001-2971-6414

Received: November 20, 2011 Accepted: April 15, 2012 Published: July 14, 2012

DOI: [10.62644/iajlb.2012.v9.i3.pp1-10](https://doi.org/10.62644/iajlb.2012.v9.i3.pp1-10)

ABSTRACT

Cold abscesses, collections of caseous material with little heat, redness or pain, are among the most recognisable soft-tissue signs of tuberculosis, and several of them appearing together in an adult with no obvious immune defect raises a harder question than any single swelling does. This narrative review asks how multifocal cold abscesses should be understood in such a person, what the published literature says about how the organism spreads, why the host sometimes fails to contain it, and how the diagnosis is established and treated. It draws on work on mycobacterial biology, granuloma immunology, extrapulmonary and miliary disease, host susceptibility, diagnostics and chemotherapy, and it reports no patient data of its own. Dissemination is best viewed as a failure of containment rather than a feature of a particular strain, and "immunocompetent" is a label that hides subtler defects: unrecognised diabetes, undernutrition, alcohol, smoking, and rare inherited abnormalities of interferon-gamma signalling. Diagnosis rests on obtaining tissue or pus for smear, culture and histology, because immune-based blood tests cannot separate active from latent infection. Treatment follows standard multidrug regimens, but abscesses may enlarge or new ones appear during effective therapy, a paradoxical reaction that is easily mistaken for failure. The review concludes that the evidence for adults without HIV is mostly descriptive and indirect, and it sets out what better reporting would contain.

Keywords: Tuberculosis; Disseminated tuberculosis; Cold abscess; Extrapulmonary tuberculosis; Immunocompetent host; Paradoxical reaction; Narrative review

Citation: Leeuwen, Santangelo and Peyrac [2012]. Disseminated Tuberculosis Presenting as Multiple Cold Abscesses in an Immunocompetent Adult: A Narrative Review. *Indo-Am. J. Life Sci. Biotechnol.* 9(3):1-10. DOI: [10.62644/iajlb.2012.v9.i3.pp1-10](https://doi.org/10.62644/iajlb.2012.v9.i3.pp1-10)

Article Class: Narrative Review

1. Introduction

Tuberculosis remains one of the leading infectious causes of death worldwide, and the picture most readers carry is of a lung

disease (1, 2). Yet a sizeable share of cases involves other organs, and the proportion outside the lung has been described as growing in some countries with otherwise



falling rates (3, 4). Among the extrapulmonary forms, the cold abscess has a special place. It is a collection of liquefied, cheese-like material that builds slowly under the skin or along a muscle plane, without the heat, redness and pain of an ordinary pyogenic abscess, and it is often the first thing the patient notices.

One cold abscess in a person with known tuberculosis is unremarkable. Several, appearing together in an adult who is not known to have any immune defect, is a different matter. It suggests that the bacillus has travelled through the blood or lymph, that it has settled in more than one place, and that the usual defences have not held. It also raises an awkward semantic point, because the word immunocompetent describes what has been checked rather than what is true. This review asks what the published literature says about how such a picture arises, how it is recognised, and how it should be treated. The aim is to describe what is known, and to be plain about what is only assumed.

The title of this article refers to a presentation that is usually reported as a single case. We do not describe a patient. No local series, hospital records or individual details are reported here, and nothing in the text should be read as drawn from the authors' own clinical practice. What follows is a narrative synthesis of work that others have published, offered so that a reader who meets such a patient can see where the evidence is firm and where it is thin.

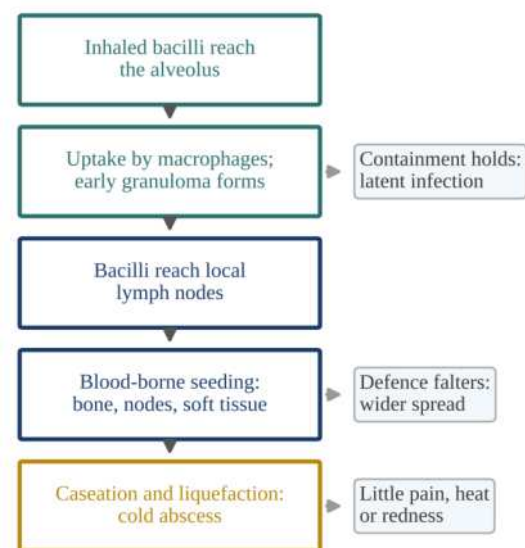
2. Literature Review

2.1 How the Bacillus Reaches a Distant Site

Infection usually begins when droplets carrying *Mycobacterium tuberculosis* reach the alveoli, where the organism is taken up by macrophages. The genome of the organism, published in 1998, showed a

bacterium that is metabolically versatile and lacks the classic toxins of many pathogens (5). Its harm comes largely from how it manipulates the host cell and the response that follows, not from a single poison (6). Figure 1 summarises the sequence from inhalation to a distant abscess in simplified form.

Inside the macrophage the bacillus resists killing and recruits further cells, which assemble into a granuloma. For a long time the granuloma was seen as the host's wall against the organism. More recent work has complicated that picture, suggesting that the structure can also serve the bacterium by providing new cells to infect and a niche in which it persists (7, 8). A reader should therefore avoid thinking of the granuloma as simply good or bad. It is a negotiated settlement, and its terms differ from one lesion to the next.



schematic, not data

Figure 1. From inhaled bacillus to a distant cold abscess: a simplified sequence (schematic, not data).

Early in infection, bacilli drain to regional lymph nodes and a few enter the bloodstream. In most people this brief seeding is silent, and the organisms settle in the apex of the lung, in nodes, in bone



and in other well-oxygenated tissues, where they may lie dormant for years (9). Reactivation at one of those sites, or a more florid blood-borne spread at the outset, is what produces extrapulmonary and miliary disease (10). Caseation follows, and as the solid material softens and liquefies, it tracks along planes of least resistance. The result is a swelling that may appear far from where the bacilli first landed. This is why the same disease can look quite different from one patient to the next.

2.2 Immune Control and Why It Fails

Control of the organism depends on cooperation between macrophages and T lymphocytes. A classic experiment in mice showed that animals lacking the gene for interferon-gamma succumbed to infection that normal mice survived (11), and subsequent reviews have placed this cytokine at the centre of a pathway that links lymphocyte signals to macrophage killing (12, 13). Later work on cell-mediated responses has added detail about which T-cell subsets contribute and how the response is regulated (14). The practical message is that anything that weakens the interferon-gamma and tumour necrosis factor axis weakens containment.

Medicine has produced several natural experiments. Patients receiving tumour necrosis factor antagonists were reported to develop tuberculosis, often extrapulmonary or disseminated, at a rate that alarmed regulators and led to routine screening before treatment (15). Infection with HIV does the same through a different route, depleting the CD4 lymphocytes on which the granuloma depends, and it shifts the spectrum of disease toward extrapulmonary forms (16, 17). These examples show what the pathway looks like when it is blocked. They also remind us that cold abscesses in a healthy-looking adult need an

explanation, and that the explanation may not yet have been found. Such differences look small one at a time, yet they decide whether a bacillus is walled off or carried on.

2.3 Risk Factors in the Apparently Healthy Adult

Between obvious immune deficiency and a genuinely normal immune system lies a large middle ground. Diabetes is the clearest example. A systematic review of observational studies found that people with diabetes had an increased risk of active tuberculosis compared with those without it, although the studies differed in design and in how the exposure was defined (18). Reviews of tobacco smoke and of alcohol use reached the same direction of conclusion, again with the caveat that confounding is hard to remove (19, 20). Undernutrition, crowding and poverty are woven through all of these, and it is difficult to separate their effects (21).

Table 1 collects these factors with a note on what to check. The list is useful, but it carries a warning. Every association in it comes from studies of groups, and none of them shows that a particular patient with disseminated disease has the factor in question. A normal glucose result does not exclude a subtle defect, and a raised one does not prove that diabetes caused the spread. The inherited defects of interferon-gamma signalling, which can cause severe mycobacterial disease in otherwise healthy people, are rare, and it would be wrong to look for them before the common causes have been excluded.

Figure 2 shows, in a qualitative way, where in the chain of containment each factor might act. The matrix is a reading aid rather than a result. Several factors are plausible at more than one step, and the evidence for the exact step involved is usually indirect. Seen this way, a negative result is a prompt to look again, not a



reason to stop looking.

Table 1. Host factors that may lie behind apparently unexplained dissemination.

Factor	What the literature shows	Worth checking
HIV infection	Strong link to extrapulmonary disease (16, 17)	HIV test in every case
Diabetes	Raised risk of active disease (18)	Glucose and glycated haemoglobin
Alcohol use	Raised risk (20)	Sensitive history
Tobacco and smoke	Raised risk, mainly respiratory (19)	Exposure history
Undernutrition and poverty	Social determinants (21)	Weight, diet, housing
Interferon-gamma pathway	Essential for control (11)	Only if no other cause is found
Tumour necrosis factor blockers	Reactivation reported (15)	Drug history

Note: The associations are drawn from the cited reviews and meta-analyses; none implies that a given patient has the factor.

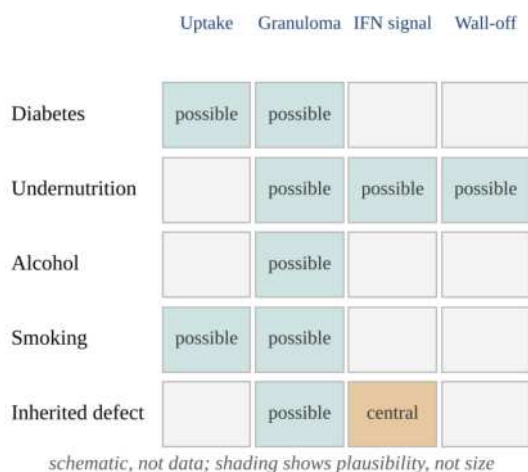


Figure 2. Where containment can fail: a qualitative matrix of host factors and the step affected (schematic, not data).

2.4 Cold Abscess at Particular Sites

Cold abscesses are seen at many sites, and the site often points to the route of spread.

Tuberculous lymphadenitis is the commonest extrapulmonary form in many settings, and when the node breaks down and discharges, the term scrofula is traditionally used (22). In the spine, infection of the vertebral bodies can give rise to a paravertebral collection that may track down the psoas sheath and present as a swelling in the groin, far from the bone that produced it (23). Soft-tissue and chest-wall abscesses occur when the bacillus reaches the tissue through the blood or by extension from pleura or ribs. Table 2 lists common sites with a practical point for each; where several are involved together, the pattern fits blood-borne dissemination and miliary disease should be considered even when the chest film looks clear (10).

Table 2. Common sites of tuberculous cold abscess and what each tends to suggest.

Site	Usual source	Practical point
Cervical and axillary nodes	Lymphatic spread, often with scrofula (22)	Needle sampling is preferred to open incision
Spine and psoas sheath	Adjacent vertebral disease (23)	Imaging defines the extent
Chest wall	Pleural or rib involvement	Deep extension may be hidden
Soft tissue of limbs	Blood-borne seeding (10)	Suggests wider dissemination
Visceral and other sites	Miliary or contiguous spread (10)	Look for a second focus

Note: Qualitative summary of the cited literature; frequencies are deliberately not given because they differ between series and settings.

3. Materials and Methods

3.1 Scope

This is a narrative review and not a systematic one. It addresses a single question: how should multifocal tuberculous cold abscesses in an adult without known immune deficiency be



understood, diagnosed and managed, according to the published literature? It is concerned with the biology of dissemination, host susceptibility, diagnostic methods and chemotherapy. It does not cover tuberculosis in children, tuberculosis in people with known HIV infection except where needed for contrast, or drug-resistant disease beyond a brief note.

3.2 Literature Assembly

Sources were chosen by the authors from the general literature on tuberculosis, with preference for reviews, meta-analyses, widely cited experimental papers and published guidelines. No formal search protocol, database list, date filter or screening procedure was applied, and no registry was consulted. Work published after 2012 was not used. Because the selection was not systematic, relevant studies may have been missed, and the choice of examples reflects the authors' judgement. None of these steps is difficult, but each is easy to skip when the diagnosis seems obvious.

3.3 Appraisal Framework

Sources were read for the question they asked, the design used, the population studied and whether conclusions followed from the data. Case reports and small series were treated as hypothesis-generating. Systematic reviews were read with attention to heterogeneity and to the possibility of publication bias. No numerical pooling was attempted, and no effect sizes are given in this article because they cannot be compared across the different designs reviewed.

4. Results

4.1 What the Literature Describes About Presentation

Reports of disseminated tuberculosis stress how variable it can be. Some patients have

fever, weight loss and night sweats, and others have little more than a lump. The abscesses themselves are typically painless or mildly tender, are slow to grow and may discharge through a sinus. A person who is otherwise well and has several of them can easily be sent first to a surgeon, and the correct diagnosis may then rest on whether anyone thinks to send the aspirate for mycobacterial culture. A clinician facing a swelling needs to know what the literature would let her say, and with what confidence.

4.2 What the Literature Describes About Diagnosis

Microbiological confirmation is the aim, and it depends on obtaining the right specimen. Pus or tissue is superior to a swab, and needle aspiration of a node or abscess is generally preferred to open incision, which risks a chronic sinus (22). Smear for acid-fast bacilli is quick but insensitive in paucibacillary specimens, culture takes weeks but permits drug-susceptibility testing, and histology showing caseating granulomas is suggestive but not specific (24). [Table 3](#) sets out these approaches and their main limitations.

Molecular tests have changed practice. A rapid automated nucleic acid assay evaluated in a large multicentre study could detect the organism and a marker of rifampicin resistance within hours in sputum specimens (25). Its value for non-respiratory specimens was still being established at the time of writing, so a negative result on pus should not by itself end the inquiry. Culture of the aspirate remains the reference point for confirming the diagnosis and for testing drug susceptibility, whatever a rapid test shows. That caution applies to every new assay. A diagnosis that rests on one negative test is not one a careful reader would trust.

**Table 3.** Diagnostic approaches for suspected tuberculous abscess and their main limits.

Approach	What it can tell	Main limit
Smear for acid-fast bacilli	Rapid hint of mycobacteria	Insensitive in pus; no species
Culture	Confirms and permits drug testing (24)	Slow; may stay negative
Histology	Caseating granuloma suggests tuberculosis	Not specific by itself
Nucleic acid test	Rapid detection, rifampicin resistance (25)	Less established outside the lung
Interferon-gamma release assay	Marks immune sensitisation (26, 27)	Cannot separate active from latent (28)
Imaging	Maps extent and deep foci	No microbiological proof

Note: Performance figures are intentionally omitted because they vary with specimen type and reference standard.

Immune-based blood tests are a source of confusion. Interferon-gamma release assays and the tuberculin skin test detect sensitisation to mycobacterial antigens, not active disease (26, 27). Systematic reviews have emphasised that these tests cannot separate latent from active infection and that their value in diagnosing active disease is limited (28). A positive result in a person with abscesses does not prove that the abscesses are tuberculous, and a negative result, particularly in an advanced or disseminated case, does not exclude them.

4.3 What the Literature Describes About Treatment

Standard treatment is a multidrug regimen given in two phases, an intensive phase with four drugs followed by a longer continuation phase with fewer, and the usual duration is extended for bone, joint

and central nervous system involvement (29). The rationale for combining drugs comes from studies of early bactericidal and sterilising activity, which show that different drugs act on different populations of bacilli (30). Management in practice also includes drainage or aspiration when an abscess is large, tense or threatens a nearby structure, though the evidence for a particular surgical approach is mostly observational (31, 32).

Adverse effects deserve respect. Liver injury is the best known, and an official statement describes how to monitor for it and when to stop drugs (33). A cohort study of patients receiving first-line therapy found that serious side effects were not rare and that they led some patients to change or stop treatment (34). Where the central nervous system is involved, adjunctive corticosteroids have been shown to improve outcome in meningitis, though that finding does not transfer automatically to other sites (35).

4.4 Paradoxical Reactions

One of the most confusing events is a paradoxical reaction, in which an existing abscess enlarges, or a new one appears, after weeks of effective therapy. The phenomenon was described in HIV-infected patients starting antiretroviral drugs, where it was named immune reconstitution disease (36, 37), and consensus definitions were later proposed for resource-limited settings (38). Similar worsening is also described in patients without HIV, and its likely basis is the recovering immune response to dead and dying bacilli. The clinical danger is that the reaction may be read as treatment failure, leading to an unnecessary change of regimen. An abscess that has been given time to settle behaves differently from one that is judged early.

Distinguishing a paradoxical reaction from true failure or drug resistance requires



cultures, drug-susceptibility results and a review of adherence. The literature gives no simple rule, and many of the descriptions are case reports. [Figure 3](#) shows a stepwise approach to a patient with several abscesses, from sampling to the decision when cultures are negative. It is a summary of how the cited sources reason and not a validated algorithm.

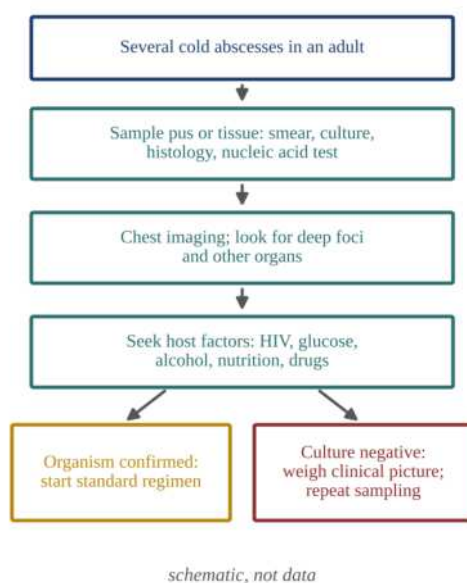


Figure 3. Stepwise approach to a patient with several cold abscesses (schematic decision pathway, not data).

5. Discussion

5.1 Interpretation

The central finding of this review is a conditional one. Several tuberculous cold abscesses in an adult are better seen as a failure of containment than as an unusual strain or a bad luck of site. What differs is the host, and the host is often incompletely examined. The word immunocompetent should therefore be treated as provisional, a statement about the tests that have been done, until HIV, diabetes, drugs, alcohol and nutrition have been addressed. That is a modest conclusion, but it is the one the published work can bear.

A third point concerns prevention. Vaccination with BCG gives uneven

protection against adult pulmonary disease, with a meta-analysis reporting wide variation between trials (39), although it appears more reliable against the severe disseminated forms in young children (40). It therefore offers little reassurance for an adult with abscesses. Efforts to develop better vaccines are ongoing but had not produced a replacement at the time of writing (41). Screening and treatment of latent infection in high-risk groups is the other preventive route, though it works best where it is targeted (42).

5.2 Limitations

The limitations of this review are considerable. Its source selection was not systematic, so the picture is partial. Most of the evidence on host factors comes from observational studies of groups, which cannot establish the cause in an individual, and nearly all of the clinical descriptions of multifocal abscesses are case reports and small series. Two of the most informative bodies of work, on paradoxical reactions and on molecular testing, were drawn largely from populations and specimens that differ from the adult with soft-tissue abscesses. Drug resistance, which can change management considerably, is touched on only briefly (43, 44). The point is not that a source is poor, only that its conclusions travel less far than its abstract implies.

5.3 Future Work

Better reporting would help more than new theory. A report of disseminated tuberculosis in an adult without known risk factors could state which tests were done to look for HIV, diabetes and other causes, what specimens were cultured and with what result, how long treatment was given, and whether any paradoxical reaction occurred and how it was judged. Prospective cohorts of adults with extrapulmonary disease, with standard



testing for host factors, would show how often the label immunocompetent survives investigation. It is a habit worth keeping even when the answer seems to be known. Studies of paradoxical reactions in patients without HIV, using explicit definitions, would also help clinicians decide when to change treatment and when to wait.

6. Conclusion

Multiple cold abscesses in an adult are a sign of tuberculosis that has spread, and they ask for a search for the reason it spread. The literature suggests a short list of causes that deserve checking, from HIV and diabetes to alcohol, undernutrition and drugs, and a longer list of rarer ones. Diagnosis depends on sampling the abscess and on culture, and immune-based blood tests cannot take that place. Treatment follows standard regimens, with the caveat that abscesses may enlarge during effective therapy. Reviews of this kind are more useful when they say where the evidence stops than when they smooth it over.

The honest summary is that the evidence for this presentation is mostly descriptive and indirect. That is not a reason for doubt about the diagnosis or the treatment, which are well supported in general. It is a reason to report such cases fully, to avoid taking one's own series as proof, and to keep the question of why the bacillus spread open until it has been answered. These points apply with equal force to many other infections that spread quietly, not only to tuberculosis.

7. Acknowledgements

The authors thank colleagues who commented on earlier drafts of this review.

8. Funding

This work received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

9. Conflict of Interest

The authors declare no conflict of interest.

10. Author Contributions

L.v.L. conceived the review and wrote the sections on host susceptibility and risk factors. G.S. wrote the sections on clinical presentation and the evidence base. C.P. wrote the sections on diagnosis and treatment. All authors revised the manuscript and approved the final version.

11. Ethics Statement

This is a review of published literature. No patients were studied and no ethical approval was required.

12. Data Availability

No new data were generated. All sources are cited in the reference list.

13. References

1. Lawn, S. D., & Zumla, A. I. (2011). Tuberculosis. *The Lancet*, 378(9785), 57–72. DOI: [10.1016/S0140-6736\(10\)62173-3](https://doi.org/10.1016/S0140-6736(10)62173-3)
2. Dye, C., Scheele, S., Dolin, P., Pathania, V., & Raviglione, M. C. (1999). Global burden of tuberculosis: Estimated incidence, prevalence, and mortality by country. *JAMA*, 282(7), 677–686. DOI: [10.1001/jama.282.7.677](https://doi.org/10.1001/jama.282.7.677)
3. Peto, H. M., Pratt, R. H., Harrington, T. A., LoBue, P. A., & Armstrong, L. R. (2009). Epidemiology of extrapulmonary tuberculosis in the United States, 1993–2006. *Clinical Infectious Diseases*, 49(9), 1350–1357. DOI: [10.1086/605559](https://doi.org/10.1086/605559)
4. Kruijshaar, M. E., & Abubakar, I. (2009). Increase in extrapulmonary tuberculosis in England and Wales 1999–2006. *Thorax*, 64(12), 1090–1095. DOI: [10.1136/thx.2009.118133](https://doi.org/10.1136/thx.2009.118133)
5. Cole, S. T., Brosch, R., Parkhill, J., Garnier, T., Churcher, C., Harris, D., ... Barrell, B. G. (1998). Deciphering the biology of *Mycobacterium tuberculosis* from the complete genome sequence. *Nature*, 393(6685), 537–544. DOI: [10.1038/31159](https://doi.org/10.1038/31159)
6. Smith, I. (2003). *Mycobacterium tuberculosis* pathogenesis and molecular determinants of virulence. *Clinical Microbiology Reviews*, 16(3), 463–496. DOI: [10.1128/CMR.16.3.463-496.2003](https://doi.org/10.1128/CMR.16.3.463-496.2003)
7. Russell, D. G. (2007). Who puts the tubercle in tuberculosis? *Nature Reviews Microbiology*, 5(1), 39–47. DOI: [10.1038/nrmicro1538](https://doi.org/10.1038/nrmicro1538)



8. Ramakrishnan, L. (2012). Revisiting the role of the granuloma in tuberculosis. *Nature Reviews Immunology*, 12(5), 352–366. DOI: [10.1038/nri3211](https://doi.org/10.1038/nri3211)
9. Barry, C. E., Boshoff, H. I., Dartois, V., Dick, T., Ehrt, S., Flynn, J., ... Young, D. (2009). The spectrum of latent tuberculosis: Rethinking the biology and intervention strategies. *Nature Reviews Microbiology*, 7(12), 845–855. DOI: [10.1038/nrmicro2236](https://doi.org/10.1038/nrmicro2236)
10. Sharma, S. K., Mohan, A., Sharma, A., & Mitra, D. K. (2005). Miliary tuberculosis: New insights into an old disease. *The Lancet Infectious Diseases*, 5(7), 415–430. DOI: [10.1016/S1473-3099\(05\)70163-8](https://doi.org/10.1016/S1473-3099(05)70163-8)
11. Flynn, J. L., Chan, J., Triebold, K. J., Dalton, D. K., Stewart, T. A., & Bloom, B. R. (1993). An essential role for interferon gamma in resistance to *Mycobacterium tuberculosis* infection. *Journal of Experimental Medicine*, 178(6), 2249–2254. DOI: [10.1084/jem.178.6.2249](https://doi.org/10.1084/jem.178.6.2249)
12. Flynn, J. L., & Chan, J. (2001). Immunology of tuberculosis. *Annual Review of Immunology*, 19, 93–129. DOI: [10.1146/annurev.immunol.19.1.93](https://doi.org/10.1146/annurev.immunol.19.1.93)
13. Kaufmann, S. H. E. (2001). How can immunology contribute to the control of tuberculosis? *Nature Reviews Immunology*, 1(1), 20–30. DOI: [10.1038/35095558](https://doi.org/10.1038/35095558)
14. Cooper, A. M. (2009). Cell-mediated immune responses in tuberculosis. *Annual Review of Immunology*, 27, 393–422. DOI: [10.1146/annurev.immunol.021908.132703](https://doi.org/10.1146/annurev.immunol.021908.132703)
15. Keane, J., Gershon, S., Wise, R. P., Mirabile-Levens, E., Kasznica, J., Schwieterman, W. D., ... Braun, M. M. (2001). Tuberculosis associated with infliximab, a tumor necrosis factor alpha-neutralizing agent. *New England Journal of Medicine*, 345(15), 1098–1104. DOI: [10.1056/NEJMoa011110](https://doi.org/10.1056/NEJMoa011110)
16. Havlir, D. V., & Barnes, P. F. (1999). Tuberculosis in patients with human immunodeficiency virus infection. *New England Journal of Medicine*, 340(5), 367–373. DOI: [10.1056/NEJM199902043400507](https://doi.org/10.1056/NEJM199902043400507)
17. Corbett, E. L., Watt, C. J., Walker, N., Maher, D., Williams, B. G., Raviglione, M. C., & Dye, C. (2003). The growing burden of tuberculosis: Global trends and interactions with the HIV epidemic. *Archives of Internal Medicine*, 163(9), 1009–1021. DOI: [10.1001/archinte.163.9.1009](https://doi.org/10.1001/archinte.163.9.1009)
18. Jeon, C. Y., & Murray, M. B. (2008). Diabetes mellitus increases the risk of active tuberculosis: A systematic review of 13 observational studies. *PLoS Medicine*, 5(7), e152. DOI: [10.1371/journal.pmed.0050152](https://doi.org/10.1371/journal.pmed.0050152)
19. Lin, H.-H., Ezzati, M., & Murray, M. (2007). Tobacco smoke, indoor air pollution and tuberculosis: A systematic review and meta-analysis. *PLoS Medicine*, 4(1), e20. DOI: [10.1371/journal.pmed.0040020](https://doi.org/10.1371/journal.pmed.0040020)
20. Lönnroth, K., Williams, B. G., Stadlin, S., Jaramillo, E., & Dye, C. (2008). Alcohol use as a risk factor for tuberculosis: A systematic review. *BMC Public Health*, 8, 289. DOI: [10.1186/1471-2458-8-289](https://doi.org/10.1186/1471-2458-8-289)
21. Lönnroth, K., Jaramillo, E., Williams, B. G., Dye, C., & Raviglione, M. (2009). Drivers of tuberculosis epidemics: The role of risk factors and social determinants. *Social Science & Medicine*, 68(12), 2240–2246. DOI: [10.1016/j.socscimed.2009.03.041](https://doi.org/10.1016/j.socscimed.2009.03.041)
22. Fontanilla, J.-M., Barnes, A., & von Reyn, C. F. (2011). Current diagnosis and management of peripheral tuberculous lymphadenitis. *Clinical Infectious Diseases*, 53(6), 555–562. DOI: [10.1093/cid/cir454](https://doi.org/10.1093/cid/cir454)
23. Rasouli, M. R., Mirkoohi, M., Vaccaro, A. R., Yarandi, K. K., & Rahimi-Movaghar, V. (2012). Spinal tuberculosis: Diagnosis and management. *Asian Spine Journal*, 6(4), 294–308. DOI: [10.4184/asj.2012.6.4.294](https://doi.org/10.4184/asj.2012.6.4.294)
24. Pai, M., Minion, J., Sohn, H., Zwerling, A., & Perkins, M. D. (2009). Novel and improved technologies for tuberculosis diagnosis: Progress and challenges. *Clinics in Chest Medicine*, 30(4), 701–716. DOI: [10.1016/j.ccm.2009.08.016](https://doi.org/10.1016/j.ccm.2009.08.016)
25. Boehme, C. C., Nabeta, P., Hilleman, D., Nicol, M. P., Shenai, S., Krapp, F., ... Perkins, M. D. (2010). Rapid molecular detection of tuberculosis and rifampin resistance. *New England Journal of Medicine*, 363(11), 1005–1015. DOI: [10.1056/NEJMoa0907847](https://doi.org/10.1056/NEJMoa0907847)
26. Pai, M., Riley, L. W., & Colford, J. M. (2004). Interferon-gamma assays in the immunodiagnosis of tuberculosis: A systematic review. *The Lancet Infectious Diseases*, 4(12), 761–776. DOI: [10.1016/S1473-3099\(04\)01206-X](https://doi.org/10.1016/S1473-3099(04)01206-X)
27. Pai, M., Zwerling, A., & Menzies, D. (2008). Systematic review: T-cell-based assays for the diagnosis of latent tuberculosis infection: An update. *Annals of Internal Medicine*, 149(3), 177–184. DOI: [10.7326/0003-4819-149-3-200808050-00241](https://doi.org/10.7326/0003-4819-149-3-200808050-00241)
28. Menzies, D., Pai, M., & Comstock, G. (2007). Meta-analysis: New tests for the diagnosis of latent tuberculosis infection: Areas of uncertainty and recommendations for research. *Annals of Internal Medicine*, 146(5), 340–354. DOI: [10.7326/0003-4819-146-5-200703060-00006](https://doi.org/10.7326/0003-4819-146-5-200703060-00006)
29. Blumberg, H. M., Burman, W. J., Chaisson, R. E., Daley, C. L., Etkind, S. C., Friedman, L. N., ... Vernon, A. (2003). American Thoracic Society/Centers for Disease Control and Prevention/Infectious Diseases Society of America: Treatment of tuberculosis. *American Journal of Respiratory and Critical Care*



- Medicine*, 167(4), 603–662. DOI: [10.1164/rccm.167.4.603](https://doi.org/10.1164/rccm.167.4.603)
30. Jindani, A., Doré, C. J., & Mitchison, D. A. (2003). Bactericidal and sterilizing activities of antituberculosis drugs during the first 14 days. *American Journal of Respiratory and Critical Care Medicine*, 167(10), 1348–1354. DOI: [10.1164/rccm.200210-1125OC](https://doi.org/10.1164/rccm.200210-1125OC)
 31. Small, P. M., & Fujiwara, P. I. (2001). Management of tuberculosis in the United States. *New England Journal of Medicine*, 345(3), 189–200. DOI: [10.1056/NEJM200107193450307](https://doi.org/10.1056/NEJM200107193450307)
 32. Frieden, T. R., Sterling, T. R., Munsiff, S. S., Watt, C. J., & Dye, C. (2003). Tuberculosis. *The Lancet*, 362(9387), 887–899. DOI: [10.1016/S0140-6736\(03\)14333-4](https://doi.org/10.1016/S0140-6736(03)14333-4)
 33. Saukkonen, J. J., Cohn, D. L., Jasmer, R. M., Schenker, S., Jereb, J. A., Nolan, C. M., ... Sharp, S. W. (2006). An official ATS statement: Hepatotoxicity of antituberculosis therapy. *American Journal of Respiratory and Critical Care Medicine*, 174(8), 935–952. DOI: [10.1164/rccm.200510-1666ST](https://doi.org/10.1164/rccm.200510-1666ST)
 34. Yee, D., Valiquette, C., Pelletier, M., Parisien, I., Rocher, I., & Menzies, D. (2003). Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 167(11), 1472–1477. DOI: [10.1164/rccm.200206-626OC](https://doi.org/10.1164/rccm.200206-626OC)
 35. Thwaites, G. E., Nguyen, D. B., Nguyen, H. D., Hoang, T. Q., Do, T. T. O., Nguyen, T. C. T., ... Farrar, J. J. (2004). Dexamethasone for the treatment of tuberculous meningitis in adolescents and adults. *New England Journal of Medicine*, 351(17), 1741–1751. DOI: [10.1056/NEJMoa040573](https://doi.org/10.1056/NEJMoa040573)
 36. Narita, M., Ashkin, D., Hollender, E. S., & Pitchenik, A. E. (1998). Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *American Journal of Respiratory and Critical Care Medicine*, 158(1), 157–161. DOI: [10.1164/ajrccm.158.1.9712001](https://doi.org/10.1164/ajrccm.158.1.9712001)
 37. Lawn, S. D., Bekker, L.-G., & Miller, R. F. (2005). Immune reconstitution disease associated with mycobacterial infections in HIV-infected individuals receiving antiretrovirals. *The Lancet Infectious Diseases*, 5(6), 361–373. DOI: [10.1016/S1473-3099\(05\)70140-7](https://doi.org/10.1016/S1473-3099(05)70140-7)
 38. Meintjes, G., Lawn, S. D., Scano, F., Maartens, G., French, M. A., Worodria, W., ... Lalloo, D. (2008). Tuberculosis-associated immune reconstitution inflammatory syndrome: Case definitions for use in resource-limited settings. *The Lancet Infectious Diseases*, 8(8), 516–523. DOI: [10.1016/S1473-3099\(08\)70184-1](https://doi.org/10.1016/S1473-3099(08)70184-1)
 39. Colditz, G. A., Brewer, T. F., Berkey, C. S., Wilson, M. E., Burdick, E., Fineberg, H. V., & Mosteller, F. (1994). Efficacy of BCG vaccine in the prevention of tuberculosis: Meta-analysis of the published literature. *JAMA*, 271(9), 698–702. DOI: [10.1001/jama.1994.03510330076038](https://doi.org/10.1001/jama.1994.03510330076038)
 40. Trunz, B. B., Fine, P., & Dye, C. (2006). Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: A meta-analysis and assessment of cost-effectiveness. *The Lancet*, 367(9517), 1173–1180. DOI: [10.1016/S0140-6736\(06\)68507-3](https://doi.org/10.1016/S0140-6736(06)68507-3)
 41. Ottenhoff, T. H. M., & Kaufmann, S. H. E. (2012). Vaccines against tuberculosis: Where are we and where do we need to go? *PLoS Pathogens*, 8(5), e1002607. DOI: [10.1371/journal.ppat.1002607](https://doi.org/10.1371/journal.ppat.1002607)
 42. Horsburgh, C. R., & Rubin, E. J. (2011). Latent tuberculosis infection in the United States. *New England Journal of Medicine*, 364(15), 1441–1448. DOI: [10.1056/NEJMc1005750](https://doi.org/10.1056/NEJMc1005750)
 43. Gandhi, N. R., Moll, A., Sturm, A. W., Pawinski, R., Govender, T., Lalloo, U., ... Friedland, G. (2006). Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *The Lancet*, 368(9547), 1575–1580. DOI: [10.1016/S0140-6736\(06\)69573-1](https://doi.org/10.1016/S0140-6736(06)69573-1)
 44. Dorman, S. E., & Chaisson, R. E. (2007). From magic bullets back to the Magic Mountain: The rise of extensively drug-resistant tuberculosis. *Nature Medicine*, 13(3), 295–298. DOI: [10.1038/nm0307-295](https://doi.org/10.1038/nm0307-295)