

Full Title: Lessons in digital epidemiology from COTS-1: coordinating multicentre research across 10 countries using operational and technology innovation to overcome funding deficiencies.

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Abstract:

There is controversy regarding diagnosis and management of ocular tuberculosis (TB) due to lack of robust evidence. The Collaborative Ocular Tuberculosis Study (COTS) was conducted in stages to enable swift, accurate data collection across 25 participating centers. Data collection was facilitated by a cloud-based data aggregation platform with programmed logic based on anecdotal evidence from uveitis experts corroborated with literature review. The platform enabled standardisation of interpretation and collection of data from patient medical records. The pre-programmed logic also ensured the platform only prompted entry of relevant data based on initial data entered for each unit of analysis. This enabled collection of the vast amounts of data without compromising either of the breadth nor the depth of data collection. The final output from this effort was an in-depth retrospective analysis to facilitate the design of future prospective investigations on ocular TB and develop best practice guidelines.

Key words: Clinical research; Methodology; Multi-center investigation; Collaborative Ocular Tuberculosis Study (COTS); ocular tuberculosis; tuberculosis

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Introduction

Tuberculosis (TB) has had an expanding global footprint¹⁻³ since the 1990s when it was reportedly the 7th commonest cause of death.⁴ Current literature describes regional differences in disease expression^{5,6} and varying reports of ocular involvement in up to 18% of patients infected with TB.⁷⁻⁹ Intraocular TB is associated with significant ocular morbidity and visual loss.^{9,10} Making matters worse, there remains unresolved controversy regarding the diagnosis and management of this disease.¹¹⁻¹⁵ It is asymptomatic in a majority of affected patients,^{7,16} and may be the first presentation of tuberculosis given that it often develops without features of systemic TB.¹⁷⁻¹⁹

The ability of intraocular TB to affect any tissue in the eye gives rise to a myriad of possible manifestations and a lack of specific symptoms/ signs.²⁰ Furthermore, investigations available at physicians' disposal have to be interpreted with caution due to limitations in specificity and sensitivity.²¹⁻²⁶ This applies even with the use of advanced techniques such as polymerase chain reaction (PCR).^{27,28} This diagnostic uncertainty leads to delay in the initiation of targeted therapy and poorer treatment outcomes¹⁵. It also contributes to the lack of universally accepted treatment guidelines as unstandardized diagnostic and treatment practices complicate the interpretation of clinical trials.^{14,15}

This study aimed to describe clinical features suggestive of intraocular tuberculosis and determine the sensitivity and specificity of investigation findings for intraocular tuberculosis. Furthermore, given the heterogeneous nature of the disease and regional differences in disease expression, this study further aims to investigate treatment outcomes of various treatment practices based on patient characteristics to shift clinical practice towards individualised management.²⁹

Methodology of the COTS-1 investigation

This study was conducted over 25 centres of diverse and international origin.³⁰ It was coordinated in Tan Tock Seng Hospital, Singapore, with ethical approval obtained by each participating centre from their local institutional ethics approval committee. The participating centres whom have contributed patients to COTS as of 2 February 2016 are detailed in **table 1**.

Inclusion criteria of patients to this study include

- 1) Availability of medical records of patients with details of ophthalmic examination are available for baseline and follow-up reviews
- 2) Relevant ancillary investigations were conducted with results available for review
- 3) Patients completed a minimum follow-up of one year
- 4) Patients are diagnosed with intraocular tuberculosis based on agreed criteria

The diagnosis of tuberculosis was conferred based on the presence of suggestive clinical features identified through a review of current literature and anecdotal evidence from the experts in this study group. The specific criteria used to diagnose intraocular tuberculosis have been detailed in earlier reports.³⁰ Patients with ocular manifestations of diseases that confound the interpretation of clinical features are excluded from this study such as patients with central serous chorioretinopathy, diabetic retinopathy, or hypertensive retinopathy. However, co-morbidities such as glaucoma or mild cataract which do not confound diagnosis or affect media clarity are not excluded.

Staged approach to platform development and study initiation

A novel web-based data entry platform was conceived to address the heterogeneous nature of this disease, based on limitations in funding and availability of dedicated, trained research manpower.³⁰ A web-based platform was designed with these considerations in mind, to minimise heterogeneity and coordinate the involvement of multiple volunteers conducting data entry at each participating center co-ordinated by the site Principle Investigator (PI). The platform provided standardised explanations of questions/data entry points, minimised the need for data cleaning, and evolved according to the data entered in earlier parts of the form for each unit of analysis (eye or patient) in order to only present relevant questions to the user.

The design and logic of the web-based platform was developed in the first center, Tan Tock Seng Hospital (TTSH, Singapore). Subsequently, it was first tested for sample collection of 10 patients' data in Moorfields Eye Hospital (London, United Kingdom) and Postgraduate Institute of Medical Education and Research (PGIMER, Chandigarh, India) to account for global variations in practice and nomenclature to facilitate accurate multinational description of this disease.³¹ Design and logic enhancements were collected from participating PIs before the platform was iteratively revised and tested subsequently in all 25 participating centers using lean start-up principles. Initial data entry was monitored for anomalies, and center PIs notified regarding any discrepancies. Subsequently interim analyses and checks were conducted by the steering committee to ascertain data quality and adherence to study procedures.

Unique benefits of the cloud-based data aggregation platform

Prompts and explanations were pegged to individual questions to guide staff involved in data entry, who were often research fellows or medical students as opposed to board-certified Ophthalmologists. This was used as a means to reinforce inclusion criteria or standardise features required to warrant a certain diagnosis/ severity grading without cluttering the entire data collection platform. **Figure 1** illustrates an example of how the form optimises data entry by changing to prompt only entry of relevant clinical signs depending on the Anatomical classification of Uveitis initially reported by the user based on the patient's medical record.

This function streamlined the collection of information that is extensive in both breadth as well as depth, without overwhelming staff involved in data entry. This was crucial for the accurate descriptions of specific phenotypes of disease, such as choroidal involvement³² and retinal vasculitis³³ that are poorly understood phenotypes of intraocular TB. In addition, the capability to mandate entry of certain information before users can progress to later sections ensures that key data points are collected and missing information minimised, since data entry staff may not always understand the importance of each finding. Missing data are a major limitation of retrospective studies as documentation and practices are not standardised. These measures helped minimise missing data, which enabled better descriptions for the results of new tests that are not yet commonly used, such as polymerase chain reaction (PCR) of intraocular fluids only used in 6% of patients in this cohort, along with the treatment and outcomes of the relevant patients.³⁴

The use of mandatory entry points also served as a control mechanism to prompt data entry staff to seek help from the PI at key points in the event they encountered uncertainties. This closes the loop on key data entry points to facilitate comprehensive description and dissemination to the academic community.³⁵ The use of multiple-choice questions for the entry of fixed data points also helps to minimise data entry errors by avoiding multiple permutations of the same given answer, while concurrently providing an avenue for free-text entry in case of exceptions. This enabled a baseline standard nomenclature to be established for this heterogeneous disease, as well as helped identify

areas requiring further expert discussion to develop a consensus on standardised reporting and nomenclature.³⁶ Ultimately, these technical innovations for the data aggregation platform improved the integrity of the dataset by minimising data cleaning and associated human errors.

Other benefits for digital epidemiology

The encrypted web-based nature of this platform has benefits that can be extrapolated to future studies, such as being able to facilitate rapid dissemination of updates to study methodology in a secure and comprehensive manner. This could be done immediately in the course of an ongoing investigation as new data became available through other new studies by reprogramming of the existing form, disseminating notices to the participating PIs, and incorporation of read receipts to ensure updates are well-received. Examples for applications of this include where a new question, investigation, or intervention may be needed, based on new evidence to prompt the entry of data.

This approach removes the hassle of disseminating multiple excel or other collection platforms, as well as reduces the subsequent human error involved in consolidating data from multiple different platforms. The encrypted nature of the form further protects patient data. As an added security measure COTS did not collate patient identifiers. Instead, patients were indexed based on study site of origin, and the last 4-5 characters of their passport number. This would only allow individuals with access to the respective hospital records and appointment dates to be able to connect the data collected to individual patients' information based on the date of initial visit.

Conclusion

The COTS group conducted a detailed retrospective review of data from around the world by using operational and technology innovation to overcome funding deficiencies. From the findings of the COTS-1 study, centres in both developing and developed world are better equipped to address this growing infectious disease threat.³¹ These lessons in digital epidemiology can be applied for future prospective studies to establish best practices for intraocular TB as well as other initiatives leveraging collaboration enabled by digital epidemiology to address underfunded research areas or rare diseases.

References

1. Murray CJ, Ortblad KF, Guinovart C, et al. Global, regional, and national incidence and mortality for HIV, tuberculosis, and malaria during 1990-2013: a systematic analysis for the Global Burden of Disease Study 2013. *Lancet*. 2014;384(9947):1005-1070.
2. Borgdorff MW, van Soolingen D. The re-emergence of tuberculosis: what have we learnt from molecular epidemiology? *Clin Microbiol Infect*. 2013;19(10):889-901.
3. Dye C, Scheele S, Dolin P, Pathania V, Raviglione MC. Consensus statement. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. WHO Global Surveillance and Monitoring Project. *Jama*. 1999;282(7):677-686.
4. Murray CJ, Lopez AD. Mortality by cause for eight regions of the world: Global Burden of Disease Study. *Lancet*. 1997;349(9061):1269-1276.
5. World, 2014 HO. Global Tuberculosis Report. www.who.int/tb/publications/global_report/en. Published 2014. Accessed 18 May 2016.
6. World, Organisatio H. Multi Drug Resistant Tuberculosis (MDR-TB). www.who.int/tb/challenges/mdr/mdr_tb_factsheet.pdf?ua=1. Published 2014. Accessed 18 May 2016.
7. Bouza E, Merino P, Muñoz P, Sanchez-Carrillo C, Yáñez J, Cortés C. Ocular tuberculosis. A prospective study in a general hospital. *Medicine (Baltimore)*. 1997;76(1):53-61.
8. Donahue HC. Ophthalmologic experience in a tuberculosis sanatorium. *Am J Ophthalmol*. 1967;64(4):742-748.
9. Biswas J, Badrinath SS. Ocular morbidity in patients with active systemic tuberculosis. *Int Ophthalmol*. 1995;19(5):293-298.
10. Basu S, Monira S, Modi RR, et al. Degree, duration, and causes of visual impairment in eyes affected with ocular tuberculosis. *J Ophthalmic Inflamm Infect*. 2014;4(1):3.
11. Gupta V, Gupta A, Rao NA. Intraocular tuberculosis--an update. *Surv Ophthalmol*. 2007;52(6):561-587.
12. Agrawal R, Gupta B, Gonzalez-Lopez JJ, et al. The role of anti-tubercular therapy in patients with presumed ocular tuberculosis. *Ocul Immunol Inflamm*. 2015;23(1):40-46.
13. Patel SS, Saraiya NV, Tessler HH, Goldstein DA. Mycobacterial ocular inflammation: delay in diagnosis and other factors impacting morbidity. *JAMA Ophthalmol*. 2013;131(6):752-758.
14. Lou SM, Montgomery PA, Larkin KL, et al. Diagnosis and treatment for ocular tuberculosis among uveitis specialists: the international perspective. *Ocul Immunol Inflamm*. 2015;23(1):32-39.
15. Lou SM, Larkin KL, Winthrop K, Rosenbaum JT, Group USS. Lack of consensus in the diagnosis and treatment for ocular tuberculosis among uveitis specialists. *Ocul Immunol Inflamm*. 2015;23(1):25-31.
16. World, Organisation H. Global Tuberculosis Control. In:2009.
17. Alvarez S, McCabe WR. Extrapulmonary tuberculosis revisited: a review of experience at Boston City and other hospitals. *Medicine (Baltimore)*. 1984;63(1):25-55.
18. Kannan B, Govindarajan K, Kummararaj S, Balaji V, Natarajapillai V. Retinal vasculitis in a patient with abdominal tuberculosis. *Oman J Ophthalmol*. 2010;3(2):81-85.
19. Morimura Y, Okada AA, Kawahara S, et al. Tuberculin skin testing in uveitis patients and treatment of presumed intraocular tuberculosis in Japan. *Ophthalmology*. 2002;109(5):851-857.
20. Gupta V, Shoughy SS, Mahajan S, et al. Clinics of ocular tuberculosis. *Ocul Immunol Inflamm*. 2015;23(1):14-24.
21. Dinnes J, Deeks J, Kunst H, et al. A systematic review of rapid diagnostic tests for the detection of tuberculosis infection. *Health Technol Assess*. 2007;11(3):1-196.

22. Wang L, Turner MO, Elwood RK, Schulzer M, FitzGerald JM. A meta-analysis of the effect of Bacille Calmette Guérin vaccination on tuberculin skin test measurements. *Thorax*. 2002;57(9):804-809.
23. Ang M, Wong WL, Kiew SY, Li X, Chee SP. Prospective head-to-head study comparing 2 commercial interferon gamma release assays for the diagnosis of tuberculous uveitis. *Am J Ophthalmol*. 2014;157(6):1306-1314; 1314.e1301-1304.
24. Mazurek GH, Zajdowicz MJ, Hankinson AL, et al. Detection of Mycobacterium tuberculosis infection in United States Navy recruits using the tuberculin skin test or whole-blood interferon-gamma release assays. *Clin Infect Dis*. 2007;45(7):826-836.
25. Vasconcelos-Santos DV, Zierhut M, Rao NA. Strengths and weaknesses of diagnostic tools for tuberculous uveitis. *Ocul Immunol Inflamm*. 2009;17(5):351-355.
26. Pollock NR, Campos-Neto A, Kashino S, et al. Discordant QuantiFERON-TB Gold test results among US healthcare workers with increased risk of latent tuberculosis infection: a problem or solution? *Infect Control Hosp Epidemiol*. 2008;29(9):878-886.
27. Sugita S, Ogawa M, Shimizu N, et al. Use of a comprehensive polymerase chain reaction system for diagnosis of ocular infectious diseases. *Ophthalmology*. 2013;120(9):1761-1768.
28. Errera MH, Goldschmidt P, Batellier L, et al. Real-time polymerase chain reaction and intraocular antibody production for the diagnosis of viral versus toxoplasmic infectious posterior uveitis. *Graefes Arch Clin Exp Ophthalmol*. 2011;249(12):1837-1846.
29. Gunasekeran DV. Association Between Noninfectious Uveitis and Psychological Stress and the Importance of Holistic Management: Treating the Patient With Uveitis as an Individual-Not a Disease. *JAMA Ophthalmol*. 2019;137(2):206-207.
30. Agrawal R, Gunasekeran DV, Grant R, et al. Clinical Features and Outcomes of Patients With Tubercular Uveitis Treated With Antitubercular Therapy in the Collaborative Ocular Tuberculosis Study (COTS)-1. *JAMA Ophthalmol*. 2017;135(12):1318-1327.
31. Agrawal R, Gunasekeran DV, Raje D, et al. Global Variations and Challenges With Tubercular Uveitis in the Collaborative Ocular Tuberculosis Study. *Invest Ophthalmol Vis Sci*. 2018;59(10):4162-4171.
32. Agrawal R, Gunasekeran DV, Agarwal A, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1: A Multinational Description of the Spectrum of Choroidal Involvement in 245 Patients with Tubercular Uveitis. *Ocul Immunol Inflamm*. 2018:1-11.
33. Gunasekeran DV, Agrawal R, Agarwal A, et al. THE COLLABORATIVE OCULAR TUBERCULOSIS STUDY (COTS)-1: A Multinational Review of 251 Patients With Tubercular Retinal Vasculitis. *Retina*. 2018.
34. Agarwal A, Agrawal R, Gunasekeran DV, et al. The Collaborative Ocular Tuberculosis Study (COTS)-1 Report 3: Polymerase Chain Reaction in the Diagnosis and Management of Tubercular Uveitis: Global Trends. *Ocul Immunol Inflamm*. 2017:1-9.
35. Testi I, Agrawal R, Mahajan S, et al. Tubercular Uveitis: Nuggets from Collaborative Ocular Tuberculosis Study (COTS)-1. *Ocul Immunol Inflamm*. 2019:1-9.
36. Agrawal R, Agarwal A, Jabs DA, et al. Standardization of Nomenclature for Ocular Tuberculosis - Results of Collaborative Ocular Tuberculosis Study (COTS) Workshop. *Ocul Immunol Inflamm*. 2019:1-11.