



CENTAUR GLOBAL NETWORK

2012-09-29-146 CGN minireviews on mycobacteria: (05) [What can be expected from mycobacteria: Latent infection](#)  
To: (04) Food-borne, water-borne and air-borne diseases; (05) Zoonoses, general; (08) Mycobacterial diseases; (22) Veterinary administration (27) [Scientific information](#)

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**CGN minireviews on mycobacteria as a public health risk**

A new series, aimed at stimulating discussion on published literature dealing with the threat to public health posed by mycobacteria. Although some information of global significance has been known for decades, the risk posed by mycobacteria remains underestimated.

Edited by the [Reference Laboratory for Paratuberculosis and Avian Tuberculosis](#) World Organization for Animal Health (OIE) and [Biomedical Technology, Epidemiology and Food Safety Global Network](#) operating in the Veterinary Research Institute, Brno, Czech Republic

We support the [One Health Initiative](#)

**(05) What can be expected from mycobacteria: Latent infection**

A comment by K. Hruska (Brno):

**Why many people do believe that all cases of Crohn's disease must follow the same scenario as salmonellosis: identifiable source – identifiable contamination of one food undoubtedly consumed – defined cluster of sufferers – successful culture and identification of pathogen – notifiable outbreak – Howgh!**

Just published in PLOS PATHOGENS

[Mycobacterium marinum causes a latent infection that can be reactivated by gamma Irradiation in adult zebrafish](#)

Mataleena Parikka, Milka M. Hammarén, Sanna-Kaisa E. Harjula, Nicholas J. A. Halfpenny, Kaisa E. Oksanen, Marika J. Lahtinen, Elina T. Pajula, Antti Iivanainen, Marko Pesu, Mika Rämetsä  
BioMediTech, University of Tampere, Tampere, Finland  
Department of Veterinary Biosciences, University of Helsinki, Helsinki, Finland  
Fimlab Laboratories, Pirkanmaa Hospital District, Tampere, Finland  
Department of Pediatrics, Tampere University Hospital, Tampere, Finland

Abstract

The mechanisms leading to latency and reactivation of human tuberculosis are still unclear, mainly due to the lack of standardized animal models for latent mycobacterial infection. In this longitudinal study of the progression of a mycobacterial disease in adult zebrafish, we show that an experimental intraperitoneal infection with a low dose (~35 bacteria) of *Mycobacterium marinum*, results in the development of a latent disease in most individuals. The infection is characterized by limited mortality (25%), stable bacterial loads 4 weeks following infection and constant numbers of highly organized granulomas in few target organs. The majority of bacteria are dormant during a latent mycobacterial infection in zebrafish, and can be activated by resuscitation promoting factor *ex vivo*. In 5–10% of tuberculosis cases in humans, the disease is reactivated usually as a consequence of immune suppression. In our model, we are able to show that reactivation can be efficiently induced in infected zebrafish by  $\gamma$ -irradiation that transiently depletes granulo/monocyte and lymphocyte pools, as determined by flow cytometry. This immunosuppression causes reactivation of the dormant mycobacterial population and a rapid outgrowth of bacteria, leading to 88% mortality in four weeks. In this study, the adult zebrafish presents itself as a unique non-mammalian vertebrate model for studying the development of latency, regulation of mycobacterial dormancy, as well as reactivation of latent or subclinical tuberculosis. The possibilities for screening for host and pathogen factors affecting the disease progression, and identifying novel therapeutic agents and vaccine targets make this established model especially attractive.

Author Summary

One third of the world's population has been estimated to be infected with *Mycobacterium tuberculosis*, which under the appropriate set of circumstances causes lethal lung disease. According to current understanding, mycobacteria can persist in their host without causing symptoms – a state referred to as latency or subclinical infection. However, if the immune system of the host becomes compromised, for example due to immunosuppressive medical treatments or HIV, the disease can become reactivated with detrimental consequences. The mechanisms leading to latency are not well



understood. Latent tuberculosis responds poorly to antibiotics, and there is currently no effective vaccine against latent or reactivated tuberculosis. Using *Mycobacterium marinum*, a natural fish pathogen and a close relative of *M. tuberculosis*, we were able to induce a disease in adult zebrafish closely mimicking the human latent disease. We show that a dormant mycobacterial population is present in animals with a latent mycobacterial disease. Dormancy is also thought to occur in human tuberculosis. In addition, we present a method, with which the latent disease can be experimentally reactivated. Despite the evolutionary distance between man and fish, the zebrafish presents itself as a unique model for studying the mechanisms related to latency and reactivation.

**Citation:**

Parikka M, Hammarén MM, Harjula S-KE, Halfpenny NJA, Oksanen KE, et al. (2012) *Mycobacterium marinum* Causes a Latent Infection that Can Be Reactivated by Gamma Irradiation in Adult Zebrafish. *PLoS Pathog* 8(9): e1002944. doi:10.1371/journal.ppat.1002944

See [CGNI web page](#) for minireviews in pdf and the references with abstracts.

**Next minireviews**

- Mycobacteria ...
- ... in vegetables
- ... in water
- ... are distributed in bottled water
- ... play a role in an Island story (ovine paratuberculosis and Crohn's disease)
- ... in the Czech Republic (Crohn's disease after the Iron Curtain had been risen)
- ... in Sardinia (T1D)
- ... in Cardiff (river Taff contaminated by MAP)
- ... in Mankanto (ill-fated swimming)
- ... can be found in every nook and cranny
- ... as secret agents (formula feeding, cold chain hypothesis, hygiene hypothesis)
- ... can, even after their death modulate inflammatory cytokines by means of their cell wall components
- ... were used for immunomodulation in Freund adjuvans already 65 years ago
- ... are pathogens as well as allergens or immunomodulators
- ... could be the missing environmental factor in many etiological hypotheses
- ... are considerably heat and chlorine resistant
- ... have unusual characteristics of food, water, and air borne pathogens or immunomodulators similar to allergens

**See the introductory documents**

- [Paratuberculosis and Crohn's disease: Premises and open questions](#)
- [Infectious diseases incorporated FUIDI premises](#)

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