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Title: Molecular epidemiology of multi- and extensively-drug-resistant *mycobacterium tuberculosis* in ireland, 2001-2014

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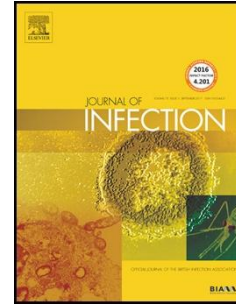
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# 1 Molecular Epidemiology of Multi- and Extensively-Drug- 2 Resistant *Mycobacterium tuberculosis* in Ireland, 2001-2014

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## 16 Highlights

- 17 • Prevalence of MDR/XDR-TB in Ireland, while low, still poses a threat to Public  
18 Health
- 19 • High lineage diversity was found among MDR/XDR-TB strains
- 20 • 'Cross-border' European Union strains have been found in Ireland
- 21 • Evidence of *in vivo* micro-evolution of strains was found during the study
- 22 • Putative transmission between an Irish-born patient and a non-Irish born patient  
23 was discovered

## 24 Abstract

25 *Objectives:* The primary objective of this work was to examine the acquisition and spread of multi-  
26 drug resistant (MDR) tuberculosis (TB) in Ireland.

27 *Methods:* All available *Mycobacterium tuberculosis* complex (MTBC) isolates (n=42), from MDR-  
28 TB cases diagnosed in Ireland between 2001 and 2014, were analysed using phenotypic drug-  
29 susceptibility testing, Mycobacterial-Interspersed-Repetitive-Units Variable-Number Tandem-Repeat  
30 (MIRU-VNTR) genotyping, and whole-genome sequencing (WGS).

31 *Results:* The lineage distribution of the MDR-TB isolates comprised 54.7% Euro-American, 33.3%  
32 East Asian, 7.2% East African Indian, and 4.8% Indo-Oceanic. A significant association was  
33 identified between the East Asian Beijing sub-lineage and the relative risk of an isolate being MDR.  
34 Over 75% of MDR-TB cases were confirmed in non-Irish born individuals and 7 MIRU-VNTR  
35 genotypes were identical to clusters in other European countries indicating cross-border spread of  
36 MDR-TB to Ireland. WGS data provided the first evidence in Ireland of *in vivo* microevolution of  
37 MTBC isolates from drug-susceptible to MDR, and from MDR to extensively-drug resistant (XDR).  
38 In addition, they found that the *katG* S315T isoniazid and *rpoB* S450L rifampicin resistance mutations  
39 were dominant across the different MTBC lineages.

40 *Conclusions:* Our molecular epidemiological analyses identified the spread of MDR-TB to Ireland  
41 from other jurisdictions and its potential to evolve to XDR-TB.

42  
43 **Keywords:** tuberculosis; molecular epidemiology; drug resistance  
44

## 45 Introduction

46 Drug resistance threatens the global management of tuberculosis [1, 2]. MDR-TB occurs when an  
47 isolate displays resistance to rifampicin and isoniazid. Extensively-drug-resistant TB displays  
48 resistance to the above plus a fluoroquinolone and a second-line injectable agent. One hundred and  
49 five countries in the world, including low-prevalence countries like Ireland, have reported XDR-TB to

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